



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 25

A. R. Katritzky &
A. J. Boulton

Advances in

Heterocyclic Chemistry

Volume 25

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

Volume 25 of *Advances in Heterocyclic Chemistry* comprises six chapters. Three of them update contributions in earlier volumes of the series: "Isoxazole Chemistry Since 1963" by B. J. Wakefield and D. J. Wright extends the review of isoxazole chemistry which appeared in Volume 2 by N. K. Kochetkov and S. D. Sokolov. J. W. Bunting's contribution "Heterocyclic Pseudobases" extends and considerably expands on the review of the same name by D. Beke in Volume 1 of the series. "The Literature of Heterocyclic Chemistry, Part II" (A. R. Katritzky and P. M. Jones) is a sequel to "The Literature of Heterocyclic Chemistry" (by A. R. Katritzky and S. M. Weeds) in Volume 7 which surveyed and classified monographs and reviews on the subject for the period 1945–1965.

Another chapter, "4-Thiazolidinones," by G. R. Newkome and A. Nayak, also updates an earlier review of the subject published elsewhere in 1961.

"Heteroaromatic Radicals, Part I: General Properties; Radicals with Group V Ring Heteroatoms" (P. Hanson) is the first of a two-part survey of heterocyclic radicals. Finally, S. Rajappa and M. D. Nair have contributed "Ring Synthesis of Heteroaromatic Nitro Compounds."

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Heterocyclic Pseudobases

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I. Introduction

The covalent addition of hydroxide ion to unsaturated heterocyclic cations in aqueous solution was first observed by Decker¹ and Hantzsch^{2,3} at the end of the nineteenth century for acridinium and quinolinium cations. Hantzsch^{2,3} coined the term pseudobase for the covalent adduct. Many of the early structural investigations on berberine, cotarnine, and related quaternary alkaloids were devoted to attempts to distinguish between the ionic hydroxide, the pseudobase, and the ring-opened amino-carbonyl tautomer as the major component in solutions of these alkaloids. Studies on alkaloidal pseudobases were reviewed by Beke⁴ in the first volume of this Series, and a more recent review,⁵ of limited scope, has also appeared. Further studies of the structures of alkaloidal pseudobases have also appeared⁶⁻¹⁴ since Beke's review⁴.

Despite the fact that the concept of pseudobase formation has "entered the folklore of heterocyclic chemistry,"¹⁵ the example presented by most heterocyclic chemistry texts of a reaction involving this phenomenon has recently been shown to be incorrect (Section V,C). It is only recently that systematic quantitative studies on pseudobase stability have been attempted or that the kinetics of pseudobase-cation equilibration have been investigated in detail. Thus, the current review covers a period in which extensive quantitative studies of pseudobase formation have become available. In addition, work in this area since Beke's earlier review⁴ has been characterized by the detailed application of spectroscopic techniques to the determination of pseudobase structure and tautomerism.

¹ H. Decker, *J. Prakt. Chem.* [N.S.] **47**, 28 (1893).

² A. Hantzsch, *Chem. Ber.* **32**, 575 (1899).

³ A. Hantzsch and M. Kalb, *Chem. Ber.* **32**, 3109 (1899).

⁴ D. Beke, *Adv. Heterocycl. Chem.* **1**, 167 (1963).

⁵ V. Šimánek and V. Preininger, *Heterocycles* **6**, 475 (1977).

⁶ J. Slavík, L. Dolejš, V. Hanus, and A. D. Cross, *Collect. Czech. Chem. Commun.* **33**, 1619 (1968).

⁷ M. A. Davis, T. A. Dobson, and J. M. Jordan, *Can. J. Chem.* **47**, 2827 (1969).

⁸ M. H. Benn and R. E. Mitchell, *Can. J. Chem.* **47**, 3701 (1969).

⁹ V. Šimánek, V. Preininger, S. Hegerová, and F. Šantavý, *Collect. Czech. Chem. Commun.* **37**, 2746 (1972).

¹⁰ V. Šimánek, V. Preininger, and J. Lasovský, *Collect. Czech. Chem. Commun.* **41**, 1050 (1976).

¹¹ Z. Gašparec and K. Weber, *Croat. Chem. Acta* **38**, 143 (1966).

¹² Z. Gašparec and K. Weber, *Croat. Chem. Acta* **39**, 175 (1967).

¹³ O. N. Tolkachev, O. E. Lasskaya, and G. A. Maslova, *Khim. Priir, Soedin.* p. 615 (1975).

¹⁴ P. W. Jeffs, *Alkaloids (N.Y.)* **9**, 41 (1967).

¹⁵ O. S. Tee and M. Endo, *Can. J. Chem.* **54**, 2681 (1976).

The concept of pseudobase formation by heteroaromatic cations is intimately related to the covalent hydration of heteroaromatic molecules¹⁶⁻¹⁹ and to Meisenheimer complex formation,²⁰⁻²⁵ although this relationship has not generally been emphasized in the literature until recently^{26,27}. All such reactions involve the formation of σ -complexes by nucleophilic addition to electron-deficient aromatic species, and yet, extensive reviews of covalent hydration¹⁶⁻¹⁹ and of Meisenheimer complex formation²⁰⁻²⁵ have neither explicitly recognized their mutual relationship nor considered pseudobase formation.

In order to keep the scope of the present review within reasonable bounds, no detailed consideration is given either to general synthetic methods involving nucleophilic addition to heterocyclic cations (e.g., carbanion addition reactions) or to anhydrobase formation reactions, which sometimes compete with pseudobase formation. However, some recent quantitative studies of anhydrobase formation are available.²⁸⁻³⁰ The preparation of this review has been complicated by the lack of a simple systematic method for searching the literature for studies of pseudobase formation. Although a comprehensive review has been attempted, I apologise in advance to any workers whose contributions in this area may have been overlooked as a result of the difficulty of carrying out a thorough literature search.

II. Spectroscopic Studies

A pH-dependent electronic spectrum for a heteroaromatic cation which contains no readily ionizable protons is usually attributable to pseudobase

¹⁶ A. Albert and W. L. F. Armarego, *Adv. Heterocycl. Chem.* **4**, 1 (1965).

¹⁷ D. D. Perrin, *Adv. Heterocycl. Chem.* **4**, 43 (1965).

¹⁸ A. Albert, *Angew. Chem., Int. Ed. Engl.* **6**, 919 (1967).

¹⁹ A. Albert, *Adv. Heterocycl. Chem.* **20**, 117 (1976).

²⁰ E. Buncl, A. R. Norris, and K. E. Russel, *Q. Rev., Chem. Soc.* **22**, 123 (1968).

²¹ P. Buck, *Angew. Chem., Int. Ed. Engl.* **8**, 120 (1969).

²² M. R. Crampton, *Adv. Phys. Org. Chem.* **7**, 211 (1969).

²³ M. J. Strauss, *Chem. Rev.* **70**, 667 (1970).

²⁴ R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.* **16**, 61 (1966).

²⁵ C. F. Bernasconi, *Org. Chem., Ser. One* **3**, 33 (1973); *Acc. Chem. Res.* **11**, 147 (1978).

²⁶ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **50**, 917 (1972).

²⁷ F. Terrier, F. Millot, and W. P. Norris, *J. Am. Chem. Soc.* **98**, 5883 (1976).

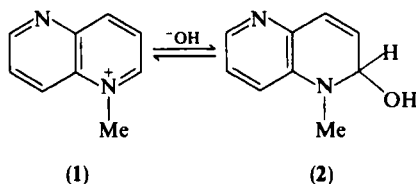
²⁸ Y. Ferré, R. Faure, É. J. Vincent, H. Larivé, and J. Metzger, *Bull. Soc. Chim. Fr.* p. 1903 (1972).

²⁹ M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2* p. 1080 (1973).

³⁰ R. A. Cox, R. Stewart, M. J. Cook, A. R. Katritzky, and R. D. Tack, *Can. J. Chem.* **54**, 900 (1976).

formation. However, when considering such a spectral change, the possibility of anhydrobase or ylid formation by deprotonation at carbon should not be overlooked. These latter phenomena are usually readily distinguishable from pseudobase formation on the basis of PMR spectral data.

In general, relatively dramatic spectral changes occur upon pseudobase formation since nucleophilic addition to an unsaturated carbon atom leads to significant changes in the electronic conjugation of the molecule, particularly if pseudobase formation disrupts the aromatic character of a ring. The pH-dependent spectrum shown in Fig. 1 for the 1-methyl-1,5-naphthyridinium cation **1** which forms the pseudobase **2** is a typical example.



The ready reversibility of such spectral changes to the spectrum of the cation upon acidification is an important test to rule out irreversible chemical reactions. In general, spectral techniques similar to those extensively used^{16,19} for the determination of the site of covalent hydration in a hetero-aromatic molecule are also applicable to the determination of the site of nucleophilic addition in pseudobase formation.

A distinction cannot be drawn between the pseudobase and its ring-opened amino-carbonyl tautomer (Section V,A) as the predominant species

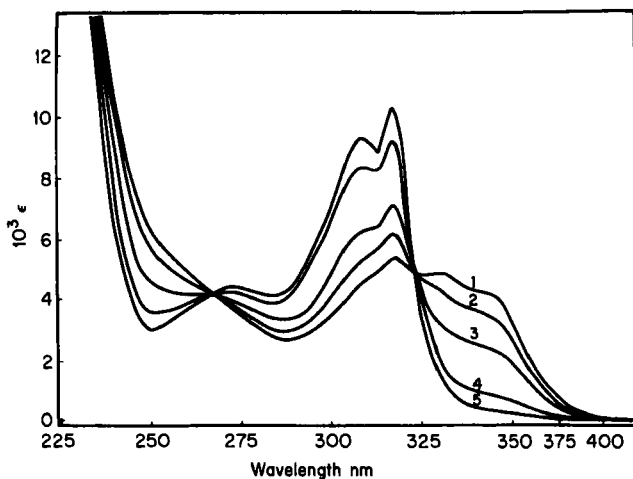


FIG. 1. The UV spectrum of 1-methyl-1,5-naphthyridinium iodide in water: (1) pH = 13.4; (2) pH = 13.0; (3) pH = 12.5; (4) pH = 12.0; (5) pH = 9.0. (From Bunting and Meathrel.²⁶)

present simply on the basis of a pH-dependent spectral change. However, a useful strategy has been developed²⁶ that allows the presence of other than minor amounts of the ring-opened tautomer to be ruled out. The methoxide adduct of a heterocyclic cation in basic methanol is incapable of undergoing ring opening. Thus, if the spectrum of the species formed from the cation in aqueous base and the spectrum of the methoxide adduct in methanol reveal no more than minor changes that are attributable to solvent effects, then the presence of the pseudobase as the major tautomer in aqueous solutions is indicated. On the other hand, a marked difference in the spectra of the cation dissolved in aqueous base and in basic methanol suggests a major contribution from the ring-opened tautomer in aqueous solutions.

Upon reduction of the heterocyclic cation with LiAlH_4 (or other metal hydride reducing agent), comparison of the spectrum of the dihydro product with that of the pseudobase is also useful as a tool for determining the presence of the ring-opened tautomer. This method is less certain than the comparison of the spectra of the hydroxide and methoxide adducts since the different electronic effects of OH and H can lead to displacements of absorption maxima. Application of these techniques has conclusively shown²⁶ that the pseudobases formed from the *N*-methyl cations of the diazanaphthalenes do not significantly tautomerize to their ring-opened tautomers in aqueous solution. The marked differences in absorption spectra of 1,2- and 1,4-dihydroquinoline derivatives³¹⁻³⁶ can also be confidently used to assign the structures of nucleophilic adducts of quinolinium and related cations.

Pseudobase formation from an unsaturated heterocyclic cation is accompanied by a significant change in the PMR spectrum. The saturation of an unsaturated carbon atom as a result of pseudobase formation results in an upfield chemical shift of approximately 4 ppm for the signal from a hydrogen atom on that carbon atom. The signals from other protons on nearby carbon atoms also undergo upfield shifts upon pseudobase formation, especially if this reaction results in the disruption of the aromatic character of a ring. Examples of the use of PMR spectral data for structural assignments of pseudobase species are available for pyridinium,³⁷ quinolinium,^{26,38}

³¹ J. W. Bunting and W. G. Meathrel, *Tetrahedron Lett.* p. 133 (1971).

³² R. Bramley and M. D. Johnson, *J. Chem. Soc.* p. 1372 (1965).

³³ E. A. Braude, J. Hannah, and R. P. Linstead, *J. Chem. Soc.* p. 3249 (1960).

³⁴ K. Sutter-Kostic and P. Karrer, *Helv. Chim. Acta* **39**, 677 (1956).

³⁵ N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.* **74**, 3671 (1952).

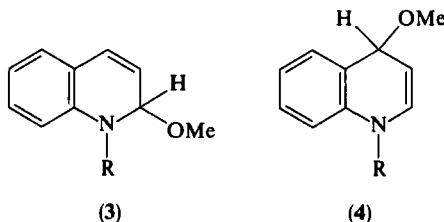
³⁶ W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.* **74**, 4517 (1952).

³⁷ O. S. Tee and M. Endo, *Can. J. Chem.* **54**, 2681 (1976).

³⁸ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 962 (1974).

isoquinolinium,^{26,38,39} naphthyridinium,²⁶ benzothioapyrylium,⁴⁰ and benzoquinolinium⁴¹ monocations and naphthyridinium^{38,42-44} and 1,10-phenanthroline^{45,46} dications. Most pseudobases are not sufficiently soluble in aqueous solution to allow PMR spectral investigation by the usual methods; however, recent advances in Fourier transform techniques of PMR spectral analysis should overcome this problem in many cases. In certain cases the pseudobases are isolable and are sufficiently stable to allow PMR spectra to be obtained in organic solvents. The PMR spectra of methoxide adducts are usually readily determined in basic methanolic solutions (preferably $\text{CD}_3\text{O}^-/\text{CD}_3\text{OD}$), and assignment of the structure of the methoxide adduct also allows assignment of pseudobase structure in the usual situation in which the electronic absorption spectra in aqueous base and basic methanol are similar.

The ever-present problem as to whether nucleophilic addition has occurred α or γ to the heteroatom in a six-atom aromatic ring is best solved via PMR spectral analysis, considering both chemical shift and coupling constant data. In particular, the 1,2- and 1,4-dihydroquinoline derivatives, **3** and **4**, which are potential methoxide adducts from quinolinium cations are readily



distinguished in favor of the former^{26,32} by the observation that $J_{2,3} = 5.0 \pm 0.5$ Hz and $J_{3,4} = 10.0 \pm 0.5$ Hz for 1,2-dihydroquinolines, whereas $J_{2,3} = 8.0 \pm 0.4$ Hz and $J_{3,4} = 4.5 \pm 1.0$ Hz for 1,4-dihydroquinolines.³² The fact that these coupling constants are essentially substituent-independent makes this method applicable to a wide range of heterocyclic cations related to the quinolinium ion. The PMR spectra of dihydro derivatives prepared by metal hydride reduction of the cations have also been useful in assigning

³⁹ J. W. Bunting and D. J. Norris, *J. Am. Chem. Soc.* **99**, 1189 (1977).

⁴⁰ I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **63**, 527 (1973).

⁴¹ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 981 (1974).

⁴² D. J. Pokorny and W. W. Paudler, *Can. J. Chem.* **51**, 476 (1973).

⁴³ J. E. Dickeson, I. F. Eckhard, R. Fielden, and L. A. Summers, *J. Chem. Soc., Perkin Trans.* **1** p. 2885 (1973).

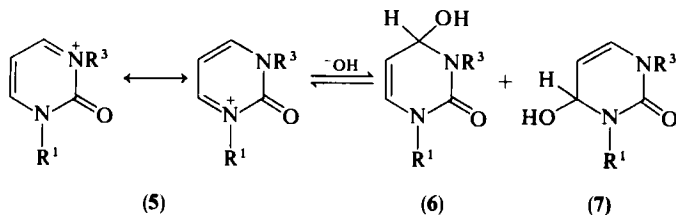
⁴⁴ J. W. Bunting, *J. Chem. Soc., Perkin Trans.* **1** p. 1833 (1974).

⁴⁵ L. A. Summers, *Tetrahedron* **24**, 5433 (1968).

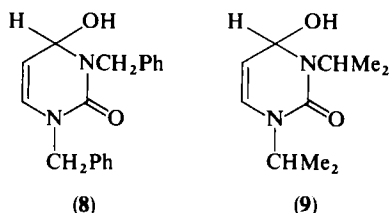
⁴⁶ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 975 (1974).

structures to these pseudobase species.^{26,31,46,47} Similar considerations are also applicable to the characterization of 1,2- and 1,4-dihydropyridines.^{48,49}

Pseudobase formation by 1,3-disubstituted 1,2-dihydro-2-oxopyrimidinium cations (**5**) has been extensively studied by UV and PMR spectroscopies.³⁷ The latter technique is particularly useful in this system in allowing the estimation of the relative amounts of **6** and **7** in the pseudobase mixture



derived from unsymmetrical cations (**5**; $R^1 \neq R^3$) and also in probing fine stereochemical details of the structures of these pseudobases. Thus, the appearance of an AB quartet ($\Delta\delta = 0.72$ ppm, $J_{AB} = 15$ Hz) for the methylene protons of the benzyl group closest to the site of the hydroxyl group in **8** clearly indicates the nonequivalence of these protons. In the pseudobase **9**,



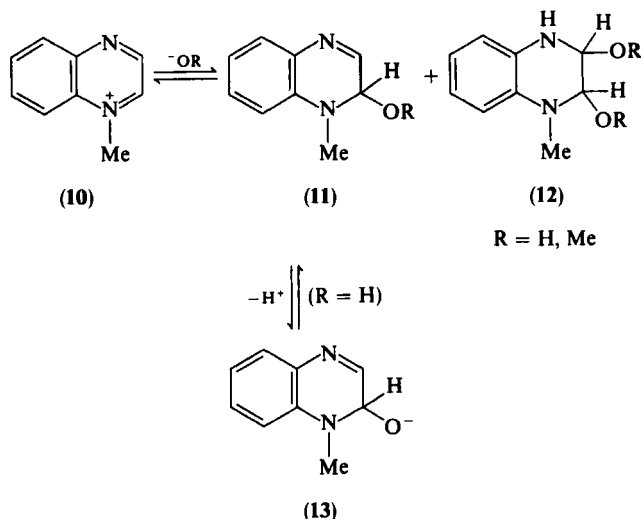
each isopropyl methyl doublet shows further fine splitting; thus diastereotopism of *both* isopropyl groups is indicated.³⁷

An interesting example of the combination of UV and PMR spectroscopies to structure determination in this area is found in the investigation²⁶ of the species present in basic solutions of the 1-methylquinoxalinium cation (**10**). The UV spectra of dilute aqueous base (pH 10.5) and basic methanol solutions of this cation are very similar: $\lambda_{\max} = 301, 340$ nm (pH 10.5); 304, 344 nm ($\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}$). In more basic aqueous solutions (pH 14.5), the only absorption maximum is at 347 nm. Two ionization constants ($\text{p}K = 8.62$ and 12.62) were obtained from the pH dependence of the UV spectrum. The PMR spectrum in 3 M NaOD/ D_2O may be readily assigned to the pseudobase anion **13**; however, the PMR spectrum in basic

⁴⁷ T. Severin, D. Batz, and H. Lerche, *Chem. Ber* **101**, 2731 (1968).

⁴⁸ H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron* **20**, 281 (1964).

⁴⁹ J. Kaválek, A. Lyčka, V. Macháček, and V. Štěrbá, *Collect. Czech. Chem. Commun.* **40**, 1932 (1975).



methanol indicates the presence of a mixture of the methoxide adduct (11; R = Me) (60%) and its covalent methanol adduct (12; R = Me) (40%). The similarity of the UV spectra of 10 in aqueous solution at pH 10.5 and in basic methanol suggests that, in dilute base 10 is present as a mixture of the pseudobase (11; R = H) and its covalent hydrate (12; R = H). The absorption maximum in the vicinity of 300 nm is typical of 1,2,3,4-tetrahydroquinoxalines, and significantly, this maximum is absent in strongly basic aqueous solutions in which PMR spectra indicate that only 13 is present.

Other cation–pseudobase equilibrations that have received detailed spectral investigation include quaternary isoquinoline alkaloids and related isoquinolinium derivatives,^{9,10} naphthyridinium mono- and dications,^{26,38,42–44,50} pyridinium cations,^{51,52} isobenzopyrylium (isochromylium) cations,⁵³ benzothiopyrylium (thiochromylium) cations,⁴⁰ and 1,3-dithiolium cations.⁵⁴ PMR spectroscopy has also been useful in the identification of pseudobases as reaction intermediates in several reactions in solution.^{55–57} While ¹³C-NMR spectroscopy is also potentially useful for the assignment of pseudobase structure, at present there do not appear to

⁵⁰ Y. Hamada, I. Takeuchi, and H. Matsuoka, *Chem. Pharm. Bull.* **18**, 1026 (1970).

⁵¹ A. G. Anderson and G. Berkelhammer, *J. Org. Chem.* **23**, 1109 (1958).

⁵² J. Kaválek, A. Lyčka, V. Macháček, and V. Štěrba, *Collect. Czech. Chem. Commun.* **40**, 1166 (1975).

⁵³ M. Vajda and F. Ruff, *Acta Chim. Acad. Sci. Hung.* **40**, 225 (1964).

⁵⁴ A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* **17**, 1931 (1969).

⁵⁵ D. Buza and J. Szymoniak, *Rocz. Chem.* **48**, 765 (1974).

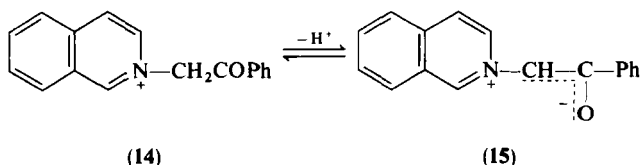
⁵⁶ A. R. Katritzky, M. Kingsland, and O. S. Tee, *J. Chem. Soc. B* p. 1484 (1968).

⁵⁷ O. S. Tee and S. Banerjee, *Can. J. Chem.* **52**, 451 (1974).

be any literature applications of this technique for this purpose for aqueous or alcoholic solutions. The addition of amide ion to pyrimidine and pyridazine derivatives in liquid ammonia solutions has been investigated by ^{13}C -NMR spectroscopy.^{58,59}

PMR and IR spectroscopies have been extensively used for the investigation of the tautomerism of pseudobases to their ring-opened amino-carbonyl isomers (see Section V,A) and for the characterization of pseudobases isolated as reaction products. There are numerous examples in the literature of the isolation of complex alcohols which can be considered as the pseudobases of quite unstable heterocyclic cations. There are now a number of examples^{50,60-63} of pseudobases being isolated under conditions which normally lead to Reissert compound formation⁶⁴ (i.e., heterocyclic base + acyl halide + KCN in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$). Thus, 5-nitroisoquinoline,^{62,63} 6-nitroquinoline,⁶³ 1,6-naphthyridine,⁵⁰ and 2-phenyl-1,3,4-thiadiazole⁶⁰ all give the pseudobases derived from the corresponding *N*-benzoyl cations when treated with benzoyl chlorides under typical Reissert conditions.

The electronic absorption spectra of solutions of the *N*-phenacyl quinolinium and isoquinolinium (**14**) cations in aqueous and methanolic base have long-wavelength maxima in the 400–500 nm region and are quite atypical of the corresponding *N*-alkyl pseudobases.³⁸ Red solids precipitate from more concentrated solutions of these cations in basic D_2O or CD_3OD . Dissolution of these red precipitates in acidic D_2O regenerates the spectra of the cations lacking the signal from the methylene protons of the phenacyl moiety. These observations suggest that the ylids (e.g., **15**) are formed preferentially to the pseudobases in these media. For the corresponding 5-nitro-2-phenacylisoquinolinium cation, the electronic absorption spectra indicate pseudobase formation in dilute solutions of the cation in both methanolic and aqueous base; however, the ylid precipitates from solution at higher concentrations.³⁸



⁵⁸ J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Org. Magn. Reson.* **7**, 86 (1975).

⁵⁹ D. E. Klinge, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **95**, 21 (1976).

⁶⁰ A. Alemagna and T. Bacchetti, *Gazz. Chim. Ital.* **102**, 1068 (1972).

⁶¹ F. D. Popp and C. W. Klinowski, *J. Chem. Soc. C* p. 741 (1969).

⁶² B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *Tetrahedron Lett.* p. 1687 (1969).

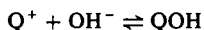
⁶³ B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J. Chem. Soc., Perkin Trans. I* p. 1146 (1974).

⁶⁴ F. D. Popp, *Adv. Heterocycl. Chem.* **9**, 1 (1968).

The formation of an anhydrobase, rather than the pseudobase, from heterocyclic cations bearing activated alkyl groups is usually readily determinable from an analysis of the PMR spectrum of the cation in basic methanol.^{41,65,66-70} The appearance of vinylic protons in the PMR spectrum in basic solutions is quite characteristic of anhydrobase formation. Spectral evidence for the rapid formation of a pseudobase, followed by a slower conversion to the thermodynamically more stable anhydrobase, has also been presented.⁴¹

III. Equilibrium Constants for Pseudobase Formation

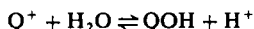
For the equilibrium between the quaternary heterocyclic cation (Q^+) and the corresponding pseudobase (QOH),



we may define an association equilibrium constant K by Eq. (1).

$$K = \frac{[QOH]}{[Q^+][OH^-]} \quad (1)$$

Alternatively, this equilibrium may be expressed as



with an equilibrium constant K_{R^+} [Eq. (2)] which has the form of a classical Brønsted acid ionization constant.

$$K_{R^+} = \frac{[H^+][QOH]}{[Q^+]} \quad (2)$$

K_{R^+} is related to the association constant K of Eq. (1) through the ionic product of water K_w by $K = K_{R^+}/K_w$. Although the symbol K_{ROH} has occasionally been used instead of K_{R^+} , the latter is preferable since it stresses the similarity of the heterocyclic cation-pseudobase equilibrium and the carbonium ion-carbinol equilibrium for which K_{R^+} was originally introduced by Deno *et al.*⁷¹

⁶⁵ G. V. Boyd and A. D. Ezekiel, *J. Chem. Soc. C* p. 1866 (1967).

⁶⁶ G. M. Clark and P. Sykes, *J. Chem. Soc. C* p. 1269 (1967).

⁶⁷ J. Metzger, H. Larivé, R. Dennilauler, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.* p. 2868 (1964).

⁶⁸ J. Metzger, H. Larivé, R. DeAnilauler, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.* p. 1266 (1969).

⁶⁹ J. J. Vorsanger, *Bull. Soc. Chim. Fr.* p. 119 (1964).

⁷⁰ W. G. Meathrel, M. Sc. Thesis, University of Toronto (1970).

⁷¹ N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Org. Chem.* **19**, 155 (1954).

Equation (2) stresses the acid-base nature of the cation-pseudobase equilibrium; and the pK_{R+} value, which is analogous to the pK_a value for a Brønsted acid, denotes the pH at which the heterocyclic cation and pseudobase are present at equal concentrations. Experimental techniques for the spectrophotometric or potentiometric determination of pK_{R+} values for pseudobase formation are identical to the methods for determination of pK_a values for Brønsted acids.⁷²

In Tables I^{26,37-41,43,46,56,73-115} and II,^{57,90,91,114,116-134} pK_{R+} values currently available for heterocyclic cations are listed in order of increasing complexity of the heterocyclic system. Aromatic and nonaromatic heterocyclic cations are considered separately in Tables I and II, respectively. Only data for strictly aqueous solutions or for aqueous solvents containing small proportions of nonnucleophilic organic solvents are included in Tables I and II. A number of data reported for aqueous alcoholic solutions are discussed separately in Section VI,A. Equilibrium constants in such media can only be considered as apparent constants since no allowance is made for the existence of the pseudobases in these solutions as mixtures of the corresponding hydroxide and alkoxide adducts. The presence of an organic solvent is sometimes necessary to promote sufficiently the solubility of the pseudobase for pK_{R+} determination. In such cases, interpretation of data relative to strictly aqueous solutions is more straightforward if non-nucleophilic cosolvents such as acetonitrile and dioxane, are chosen in preference to alcohols.

The temperature dependence of pK_{R+} has been reported⁹² for three heteroaromatic cations over the range 15°–55°. The use of pK_{R+} to assess

⁷² A. Albert and E. P. Serjeant, "The Determination of Ionization Constants," 2nd ed. Chapman & Hall, London, 1971.

⁷³ R. G. Yount and D. E. Metzler, *J. Biol. Chem.* **234**, 738 (1959).

⁷⁴ P. Haake and J. M. Duclos, *Tetrahedron Lett.* p. 461 (1970).

⁷⁵ K. Hirai, *Tetrahedron* **27**, 4003 (1971).

⁷⁶ A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* **18**, 865 (1970).

⁷⁷ K. Wallenfels and W. Hanstein, *Justus Liebigs Ann. Chem.* **709**, 151 (1967).

⁷⁸ R. B. Martin and J. G. Hull, *J. Biol. Chem.* **239**, 1237 (1964).

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⁸⁰ A. Williams, *J. Am. Chem. Soc.* **93**, 2733 (1971).

⁸¹ I. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 243 (1965).

⁸² A. R. Katritzky, M. Kingsland, and O. S. Tee, *Chem. Commun.* p. 289 (1968).

⁸³ H. Vorsanger, *Bull. Soc. Chim. Fr.* p. 551 (1967).

⁸⁴ I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **58**, 263 (1968).

⁸⁵ A. V. El'tsov, A. I. Grigor'eva, and I. Ya. Kvitko, *J. Org. Chem. USSR (Engl. Transl.)* **10**, 1143 (1974).

⁸⁶ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 303 (1974).

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⁸⁸ B. J. Huckings and M. D. Johnson, *J. Chem. Soc.* p. 5371 (1964).

TABLE I: pK_R^+ VALUES FOR HETEROAROMATIC CATIONS^a

Cation	pK_R^+	Reference	References to pK_R^+ for other substituted cations
3-A-4-Me-Oxazolium ^b	5.8	73	73
3,5-Dimethylthiazolium	10.8	74	
4-Phenyl-1,3-dithiolium	2.2, 2.10	75, 76	75, 76
1-Methyl-3,5-dicyanopyridinium	3.5	77	77–79
2,4,6-Trimethylpyrylium (23 ; $R^2 = R^4 = R^6 = \text{Me}$)	6.7 ^{c,d}	80	80
Thiopyrylium	> 6	81	
1,3-Dimethyl-2-oxopyrimidinium (5 ; $R^1 = R^3 = \text{Me}$)	7.03, 7.11	37, 56, 82	37
3-Methylbenzothiazolium (78 ; $R = \text{H}$)	8.30 ^{c,e}	83	83
Thieno[2,3- <i>b</i>]thiopyrylium	6.3	84	
Thieno[3,2- <i>b</i>]thiopyrylium	7.0	84	
^f	0.29	85	
1-Methylquinolinium	~ 16.5	26	38, 39, 86, 87
1-Cyanoquinolinium	–0.86, –1.05	87, 88	87
1-Methyl-3-nitroquinolinium (34)	6.74, 6.82 ^g	26, 86	
	9.16 ^h	86	
1-Methyl-4-nitroquinolinium	5.31	89	
2-Methylisoquinolinium	~ 15.3, 16.29 ⁱ	26, 90, 91	26, 38, 39, 46, 87, 88, 92
2-Cyanoisoquinolinium	–2.10	88	87
Benzopyrylium (20 ; $X = \text{O}$)	–1.96	81, 93	93–96
Benzothiopyrylium (20 ; $X = \text{S}$)	3.15	40, 81, 97	40, 97
Isobenzothiopyrylium	2.17	81, 98	98
1-Selenanaphthalenium (20 ; $X = \text{Se}$)	1.20	81	
2-Selenanaphthalenium	0.20	99	
2-Methylphthalazinium (119)	11.04	26	
1-Methylquinoxalinium (10)	8.62	26	
3-Methylquinazolinium	≤ 7	26	100
1-Methyl-1,5-naphthyridinium (1)	12.67	26	
1,5-Dimethyl-1,5-naphthyridinium ^j	4.93, 5.2	38, 43	
6-Methyl-1,6-naphthyridinium	12.33	26	
1,6-Dimethyl-1,6-naphthyridinium ^j	2.15	38	
7-Methyl-1,7-naphthyridinium	13.1	26	
1-Methyl-1,8-naphthyridinium	12.44	26	38
5,6-Dihydroimidazo[1,2,3- <i>ij</i>][1,8]naphthyridinium ^j	~ 2.2	43	

2-Methyl-2,7-naphthyridinium	10.52	38	
2,7-Dimethyl-2,7-naphthyridinium ^j	3.84	38	
10-Methylacridinium	9.75, 9.86	26, 101	41, 92, 102, 103
5-Methylphenanthridinium	10.4, 11.94	41, 104	41, 104
Acridizinium	~ 8	105	
Xanthylium (22; X = O)	-0.83	81	106
Thioxanthylium (22; X = S)	-0.21	81	
21 (X = O)	-5.96	81	
21 (X = S)	-1.67	81	
21 (X = Se)	-4.28	81	
1-Thiaanthracenium	1.14	107	
2-Thiaanthracenium	0.33	107	
1-Selenaphenanthrenium	2.70	108	
2-Selenaphenanthrenium	1.97	108	
3-Selenaphenanthrenium	2.39	108	
4-Selenaphenanthrenium	1.88	108	
37	9.9	109	
17	9.54	46	
18	9.17	46	
137	8.31	110, 111	111
3,5-Dimethylumiflavinium	4.15, 4.1	112, 113	
k	6.7	114	
Pyrazino[1,2,3,4- <i>lmn</i>]-1,10-phenanthroline	~ 6.8, 6.22	46, 115	
l	9.05	106	

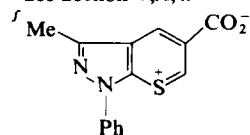
^a In aqueous solution at 20°–25°.

^b A = 2-methyl-4-amino-5-pyrimidinylmethyl.

^c From kinetic measurements.

^d See Section V,A,1.

^e See Section V,A,4.

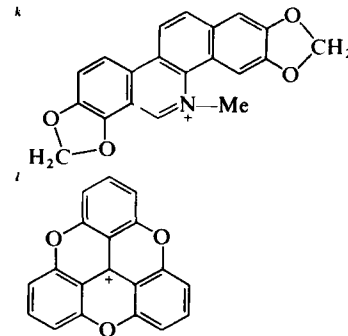


^g C-4 pseudobase.

^h C-2 pseudobase.

ⁱ In dimethyl sulfoxide–water.

^j Dication.



References continued from page 11.

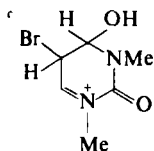
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⁹⁰ M. J. Cook, A. R. Katritzky, A. D. Page, R. D. Tack, and H. Witek, *Tetrahedron* **32**, 1773 (1976).
⁹¹ M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron Lett.* p. 5019 (1972).
⁹² J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **51**, 1965 (1973).
⁹³ G. Canalini, I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **57**, 1045 (1967).
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⁹⁸ G. Canalini, I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **61**, 504 (1971).
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¹⁰³ M. M. Rauhut, D. Shechan, R. A. Clarke, B. G. Roberts, and A. M. Semsel, *J. Org. Chem.* **30**, 3587 (1965).
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¹⁰⁷ I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **61**, 662 (1971).
¹⁰⁸ I. Degani and R. Fochi, *Ann. Chim. (Rome)* **63**, 319 (1973).
¹⁰⁹ D. J. Norris, J. W. Bunting, and W. G. Meathrel, *Can. J. Chem.* **55**, 2601 (1977).
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¹¹¹ J. Clark and B. Parvizi, *J. Chem. Soc., Perkin Trans. 1* p. 131 (1976).
¹¹² C. Kemal and T. C. Bruice, *J. Am. Chem. Soc.* **98**, 3955 (1976).
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¹¹⁶ J. Hine, *J. Am. Chem. Soc.* **93**, 3701 (1971).
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¹²⁶ A. Fabrycy, K. Grabowski, and M. Kaminska, *Rocz. Chem.* **51**, 1081 (1977).
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¹²⁹ L. A. Pavlova and I. V. Samartseva, *J. Org. Chem. USSR (Engl. Transl.)* **2**, 1686 (1966).
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¹³¹ L. A. Pavlova and V. S. Sorokina, *J. Org. Chem. USSR (Engl. Transl.)* **4**, 698 (1968).
¹³² L. A. Pavlova, *J. Org. Chem. USSR (Engl. Transl.)* **1**, 1858 (1965).
¹³³ H. Glinka and A. Fabrycy, *Rocz. Chem.* **44**, 1703 (1970).
¹³⁴ B. Skinner, *J. Chem. Soc.* p. 823 (1950).

TABLE II
 pK_R VALUES FOR NONAROMATIC HETEROCYCLIC CATIONS^a

Cation	pK_R	Reference	References to pK_R for other substituted cations
$\text{Me}_2\text{C}=\text{NHMe}^+$	8.09 ^b	116	
$\text{Me}_2\text{C}=\text{NHOH}^+$	7.62 ^b	116	
$\text{Me}_2\text{CHCH}=\text{NHMe}^+$	8.31 ^b	116	
2,2-Dimethyl-3,5-diphenyl-2H-furylium	2.97	117	117
1,3-Diphenylimidazolium (63)	12.2 ^b	118, 119	
^c	< -2	57	
1,2,2,5,5-Pentamethyl-2,5-dihydropyrazinium	> 9.5	120	
1,1-Dimethyl-2,3-diphenyl-1H-isoindolium	10.44 ^d	121	121, 122
1,1,3-Trimethyl-1H-isobenzofurylium	-2.46	123	123-133
2-Methyl-3,4-dihydroisoquinolinium	10.75, 10.9	90, 91, 114	114, 134

^a In aqueous solution at 20°–25° unless otherwise stated.

^b From kinetic measurements.



^d In 20% acetone in water.

the temperature dependence of cation–pseudobase equilibration is complicated by the relatively pronounced temperature dependence of the ionic product of water (K_w).¹³⁵ For this reason, the association constant K [Eq. (1)] gives a more realistic measure of the temperature sensitivity of pseudobase formation from a cation. Use of $\log K$ ($pK_w - pK_R$) in a van't Hoff plot allows the estimation of the thermodynamic parameters for cation–pseudobase equilibration. Values of $\Delta H^\circ = -10.8 \text{ kcal mol}^{-1}$ and $\Delta S^\circ = +4.5 \text{ cal mol}^{-1} \text{ deg}^{-1}$ have been obtained for pseudobase formation from the 2-methyl-4-nitroisoquinolinium cation, and $\Delta H^\circ = -2.9 \text{ kcal mol}^{-1}$ and $\Delta S^\circ = +8.7 \text{ cal mol}^{-1} \text{ deg}^{-1}$ for the 10-methyl-acridinium cation.⁹²

Pseudobase formation in H_2O and D_2O has been quantitatively compared⁹² for the 2-methyl-4-nitroisoquinolinium cation. At 25° and ionic strength 0.1, $pK_R(\text{H}_2\text{O}) = 5.11$ and $pK_R(\text{D}_2\text{O}) = 5.73$. Thus under these conditions, $K(\text{H}_2\text{O})/K(\text{D}_2\text{O}) = 0.56$.

¹³⁵ H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.* **36**, 973 (1940).

The data in Tables I and II may be analyzed in a number of ways: nature and number of heteroatoms, size of the heteroaromatic system, substituent effects, etc. Attempts at such analyses of the relationships between pK_R^+ and the structure of the cation are presented in the following sections. As expected, the most general observation is that the most electron-deficient cations are most susceptible to pseudobase formation and have the lowest pK_R^+ values.

A. AROMATIC CATIONS

1. Nitrogen Heterocycles

There is no spectral evidence for pseudobase formation by the *N*-methylpyridinium cation in even the most basic aqueous solutions that are attainable. An oil which separates from solutions of this cation in concentrated aqueous base has been identified by PMR and IR spectroscopies as predominantly ionic *N*-methylpyridinium hydroxide.⁷⁰ The UV spectra of the *N*-methylquinolinium and *N*-methylisoquinolinium cations are pH-independent below pH 14, but both these cations undergo irreversible reactions in more basic aqueous solutions (Section V,D) so that pK_R^+ values are not directly measurable. Based on substituent effects in more highly substituted quinolinium and isoquinolinium cations, pK_R^+ values of 16.5 and 15.3 have been estimated²⁶ for the *N*-methylquinolinium and *N*-methylisoquinolinium cations respectively. The estimate for the latter cation is based on somewhat limited data and should be compared with $pK_R^+ = 16.29$, which has been measured in aqueous dimethyl sulfoxide solutions.^{90,91}

Further benzologation leads to measurable pK_R^+ values for the *N*-methylacridinium (9.86²⁶) and *N*-methylphenanthridinium (11.94⁴¹) cations; however, $pK_R^+ > 14$ in aqueous solutions of the *N*-methyl cations of both the 5, 6- and 7, 8-benzoquinolines.⁴¹ The loss in resonance energy upon pseudobase formation is expected to be one of the major factors involved in considerations of the relative susceptibilities of heterocyclic cations to pseudobase formation. A rather crude, but informative, calculation of the loss in resonance energy (ΔR) upon pseudobase formation has been attempted for each of the above cations.

The details of the estimates of the loss of resonance energy upon pseudobase formation are outlined in Table III.¹³⁶⁻¹³⁹ These estimates are based

¹³⁶ R. C. Weast, ed. "Handbook of Chemistry and Physics," 57th ed. p. D147. Chem. Rubber Publ. Co., Cleveland, Ohio, 1976-1977.

¹³⁷ A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.* p. 2240 (1948).

¹³⁸ M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.* **44**, 759 (1966).

¹³⁹ G. M. Badger, "Aromatic Character and Aromaticity," p. 45. Cambridge Univ. Press, London and New York, 1969.

TABLE III
ESTIMATES OF LOSS OF RESONANCE ENERGY ON PSEUDOBASE FORMATION

Heterocycle	pK_a	pK_R for N—Me cation	Resonance energy ^a of heterocycle (kcal mol ⁻¹)	Pseudobase reference molecule	Resonance energy ^b of pseudobase reference	ΔR (kcal mol ⁻¹)
Pyridine	5.35 ^c	$\gg 16$	19.2	—	0	19
Quinoline	4.90 ^c	~ 16.5	41.0	Benzene	36.0	5
Isoquinoline	5.42 ^c	~ 15.3	41.4	Benzene	36.0	5
5,6-Benzoquinoline	5.11 ^d	> 14	68.2	Naphthalene	61.0	7
7,8-Benzoquinoline	4.21 ^d	> 14	68.3	Naphthalene	61.0	7
Phenanthridine	5.58 ^c	11.94	67.8	2 \times Benzene	72.0	-4
Acridine	5.58 ^c	9.86	59.2	2 \times Benzene	72.0	-13

^a From Dewar and Gleicher.¹³⁸

^b From Badger.¹³⁹

^c From Weast.¹³⁶

^d From Albert *et al.*¹³⁷

on calculated resonance energies for the heterocycles¹³⁸ and measured heats of combustion of the aromatic hydrocarbons.¹³⁹ The following assumptions have been made:

(1) Since resonance energies for the cations themselves are not available, the resonance energies of the corresponding neutral bases have been employed. This apparently gross approximation can be justified by the observation that there is little difference among the pK_a values for protonation of these heterocyclic bases (Table III). This suggests that the differences in resonance energy between the neutral base and its cation are approximately the same for each heterocycle, and hence the *relative* order of the resonance energies of the *N*-methyl cations should be the same as that of the parent base.

(2) The resonance energy of the pseudobase has been approximated by that of the nearest aromatic molecule from which it can be considered to be derived. Thus, benzene is used as the reference molecule for 1,2-dihydro-2-hydroxy-1-methylquinoline, etc. Small differences in the resonance energies of benzene and aniline ($1.6 \text{ kcal mol}^{-1}$)¹⁴⁰ and benzene and styrene etc. have been ignored.

The calculated order of ΔR is pyridinium > quinolinium \approx isoquinolinium \approx 5,6-benzoquinolinium \approx 7,8-benzoquinolinium > phenanthridinium > acridinium, which is the same as the order of pK_{R+} values insofar as they are available. Although the absolute magnitudes of ΔR in Table III are not definitive (due mainly to the unknown difference in the resonance energies of the cations and the corresponding neutral bases), these approximate calculations do qualitatively reflect the observed order of susceptibility of these cations to pseudobase formation. In particular, although the *N*-methylacridinium, -phenanthridinium, and -benzoquinolinium cations might all be expected to have similar resonance energies, the acridine and phenanthridine pseudobases have an advantage over the less stable isomeric benzoquinoline pseudobases which arises from the difference in the total resonance energy of two isolated benzene rings (36 kcal mol^{-1} per ring) relative to the resonance energy of naphthalene ($30.5 \text{ kcal mol}^{-1}$ per ring).

The preceding approximation method, though relatively crude, may also be useful for qualitatively predicting the relative susceptibilities of other heteroaromatic cations to nucleophilic addition reactions and also the relative ease of hydrogen transfer between various heterocyclic molecules.¹⁴¹

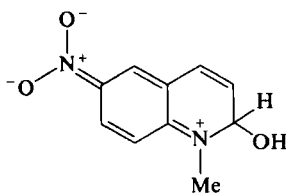
Introduction of electron-withdrawing substituents destabilizes the cation relative to the pseudobase and results in the lowering of pK_{R+} relative to

¹⁴⁰ N. L. Allinger, M. P. Cava, D. C. Dejongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, "Organic Chemistry," p. 239. Worth Publ. New York, 1971.

¹⁴¹ E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.* p. 3268 (1960).

the parent cation. There are numerous examples of this phenomenon in Table I for substituents both on the quaternary nitrogen atom and on ring carbon atoms. Probably the most dramatic indication of this effect is the value $\Delta pK_R^+ = 17.5$ between the *N*-methyl- and *N*-cyanoquinolinium cations. As expected, substituents that are present on the ring that is susceptible to hydroxide ion addition have a much greater effect on pK_R^+ than substituents that are farther removed. [Compare pK_R^+ for the 3- and 4-nitro-1-methylquinolinium cations (6.8^{26,86} and 5.3,⁸⁹ respectively) with the corresponding 5-, 6-, 7-, and 8-nitro derivatives (9.7–12.3^{38,87}).] In a number of cases, quantitative correlations of substituent effects on pK_R^+ have been attempted; these are summarized in Section III,C.

Introduction of additional ring nitrogen atoms also results in the destabilization of the cation relative to the pseudobase and, consequently, a reduction in pK_R^+ . The general observation that the electronic effect of a pyridine-type ring-nitrogen atom is approximately equal to that of a nitro group at the same position in the corresponding homocyclic ring appears to be a reasonable guide (compare pK_R^+ for *N*-methylnitroquinolinium cations and the analogous *N*-methyldiazanaphthalene cations).^{26,38,87}



(16)

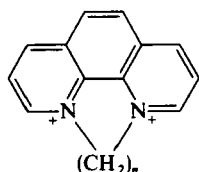
In several cases, specific resonance or steric effects result in relatively small deviations from this general rule. Thus, the pseudobase of the 1-methyl-6-nitroquinolinium cation is stabilized by the resonance contributor **16** that is not available in the case of the corresponding (unknown) 1-methyl-1,6-naphthyridinium cation. The 1,8-peri interaction in 1-alkyl-8-nitroquinolinium cations is considerably relieved in the corresponding pseudobase in which the N-1 and C-8 substituents are no longer coplanar; consequently, pK_R^+ for the 1-methyl-8-nitroquinolinium cation (9.67³⁸) is considerably smaller than for the 1-methyl-1,8-naphthyridinium cation (12.44²⁶). Some of this difference may also be attributable to resonance stabilization analogous to **16**. The pK_R^+ values are not directly measurable for cations such as the 3-methylquinazolinium cation^{142,143} which readily form covalent hydrates. This consideration will be expected to prevent the measurement

¹⁴² A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* p. 5267 (1961).

¹⁴³ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **48**, 3449 (1970).

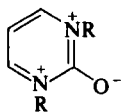
of pK_R^+ values for most cations derived from tri- and tetraazanaphthalenes.^{16,17,19}

The extremely electron-deficient heteroaromatic dications produced by quaternization of both ring nitrogen atoms of the naphthyridines very readily form pseudobases in aqueous solution. The data of Table I indicate that pK_R^+ values for *N,N'*-dimethylnaphthyridinium dications are 7–10 units lower than for the corresponding *N*-methylnaphthyridinium monocations. The *N,N'*-bridged 1,10-phenanthroline dications **17** and **18** also have considerably lower pK_R^+ values than the *N*-methyl-1,10-phenanthroline



(17) $n = 2$ (18) $n = 3$

cation. The greater susceptibility of **18** than **17** to pseudobase formation has been suggested⁴⁶ to arise from the release of strain in **18** upon pseudobase formation. The $pK_R^+ \sim 7$ observed³⁷ for 1,3-dialkyl-1,2-dihydro-2-oxo-pyrimidinium cations is most simply explained in terms of a major contribution from the mesomeric form **19** to the electronic structures of these monocations.


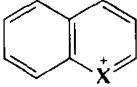
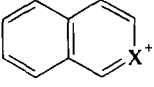
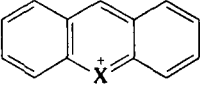
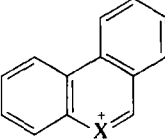


(19)

2. Oxygen, Sulfur, and Selenium Heterocycles

Heteroaromatic cations containing oxygen, sulfur, or selenium ring heteroatoms are far more susceptible to pseudobase formation than the corresponding *N*-methyl cations. A comparison of data for structurally related cations is given in Table IV. It is clear that in most cases pK_R^+ values fall in the order $O < Se < S \ll NMe$, and a linear relationship of unit slope exists between pK_R^+ values for at least two series (**20** and **21**) of cations (Fig. 2). The pK_R^+ values reported⁸¹ for the linear tricyclic system **22** are unusual in that they fall in the order $Se < O < S$ and furthermore suggest that in these cases **22** are less susceptible to pseudobase formation than their isomers **21**, which is unexpected in view of the relative pK_R^+

TABLE IV
COMPARISON OF pK_{R+} VALUES FOR NITROGEN, OXYGEN,
SULFUR, AND SELENIUM HETEROCYCLIC CATIONS^a

Cation	X = O	X = S	X = Se	X = NMe
	<5	>6		>>16
	-1.96	3.15	1.20	~16.5
		2.17	0.20	~15.3
	-0.83	-0.21	-1.67	9.86
	-5.96	-1.67	-4.28	11.94

^a See Table I for references to determination of pK_{R+} .

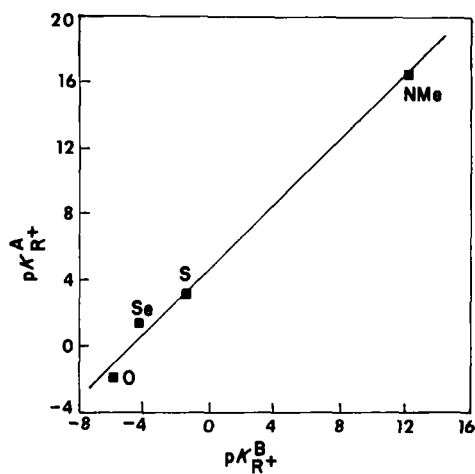
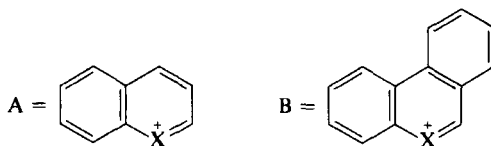
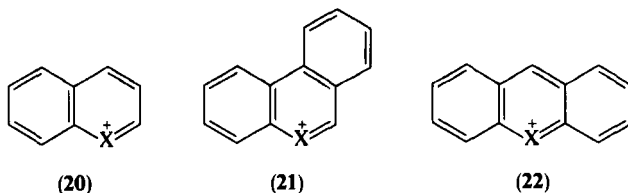


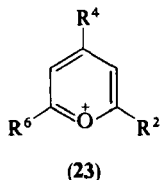
FIG. 2. Relationship between pK_{R+} for cations A and B for various X. Line has slope 1.





values for the *N*-methylacridinium and *N*-methylphenanthridinium cations that were successfully rationalized above (Table III).

Pseudobase formation by the pyrylium, thiopyrylium, and selenopyrylium cations is complicated by ring-opening reactions (Section V,A) which preclude a simple direct measurement of pK_{R^+} for these cations. In a kinetic study, Williams⁸⁰ has found the ring opening of 2,4,6-trisubstituted pyrylium cations **23** to be controlled by pK_a values in the range of 5.0–6.7 for R^2 ,



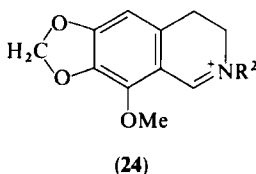
R^4 , R^6 = Me or Ph. These pK_a values were not assigned, and the most likely explanation is that these are actually pK_{R^+} values for pseudobase formation by these cations. Such an assignment indicates that pK_{R^+} is somewhat less than 5 for the unsubstituted pyrylium cation which is consistent with $pK_{R^+} > 6$ which has been estimated⁸¹ for the thiopyrylium cation.

Various isolated examples of pK_{R^+} values for other heteroaromatic systems are given in Table I. The similarity in pK_{R^+} values for the isomeric 1-, 2-, 3-, and 4-selenaphenanthrene cations further supports the preceding inference that the change in resonance energy upon pseudobase formation is the major determinant of pK_{R^+} .

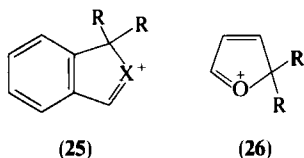
B. NONAROMATIC HETEROCYCLIC CATIONS

As indicated in Table II, only scattered data are available for nonaromatic heterocyclic cations; however, some trends are apparent. If one assumes that a pK_{R^+} of ~ 8 , as indicated for the first three cations in Table II, is typical of an isolated $\text{>C}=\text{N}^+\text{<}$ bond, then any stabilization of such cationic systems via resonance or other electronic effects would be expected to result in higher pK_{R^+} values. Thus, $pK_{R^+} > 8$ is observed for the 1,3-diphenylimid-

azolium cation^{118,119} which is stabilized by distribution of positive charge on both nitrogen atoms via two equivalent resonance structures and also for the 2-methyl-3,4-dihydroisoquinolinium cation^{90,91,114} which displays benzylic carbonium ion resonance stabilization. This latter cation has pK_R^+ approximately 4.5 units smaller than that estimated²⁶ for its aromatic analog, the 2-methylisoquinolinium cation. The lower pK_R^+ value for the 2-phenyl-3,4-dihydroisoquinolinium cation (**24**; $R^2 = \text{Ph}$) than its 2-methyl analog (**24**; $R^2 = \text{Me}$) ($\Delta pK_R^+ (\text{Me} - \text{Ph}) \approx 4$)^{114,134} is presumably a reflection of the aniline-type resonance stabilization in the pseudobase of the *N*-phenyl derivative which is not available in the *N*-methyl cation.



The increased susceptibility to pseudobase formation for O-heterocyclic relative to the corresponding N-heterocyclic cations that was noted above for the aromatic series is also seen in the 1*H*-isobenzofurylium (**25**; $X = \text{O}$) and *N*-phenyl 1*H*-isoindolium (**25**; $X = \text{NPh}$) series in Table II. For these cases $\Delta pK_R^+ (\text{NPh} - \text{O}) \approx 11.5$, which may be converted to $\Delta pK_R^+ (\text{NMe} - \text{O}) \approx 15.5$ using the difference noted previously for *N*-methyl- and *N*-phenyl-3,4-dihydroisoquinolinium derivatives. This difference is in reasonable agreement with $\Delta pK_R^+ (\text{NMe} - \text{O}) \approx 18.5$ observed for aromatic cations (Table IV). The low stability of the cation relative to the pseudobase for O-heterocycles is also present in the 2*H*-furylium cations (**26**). Although



a direct comparison is not possible on the basis of currently available data, $\Delta pK_R^+ (\text{26} - \text{25}, X = \text{O})$ seems to be consistent with the expected effect of benzologation discussed in Section III,A.

C. LINEAR FREE ENERGY RELATIONSHIPS

A number of attempts have been made to correlate pK_R^+ for pseudobase formation with substituent effects expressed as Hammett σ or Taft σ^* values.

TABLE V
LINEAR FREE ENERGY RELATIONSHIPS FOR CATION-PSEUDOBASE EQUILIBRATION^a

X-Substituted cation	Correlation equation	Number of substituents	Correlation coefficient	Reference
1-X-3-Methyl-2-oxypyrimidinium	(3) $pK_R^+ = -3.60\sigma_X^+ + 7.1$	7	0.985	37
1-(X-Benzyl)-5-nitroquinolinium	(4) $pK_R^+ = -4.0\sigma_{CH_2C_6H_4X}^+ + 12.25$ (4a) $pK_R^+ = -1.32\sigma_X + 11.38$	7	0.983	39
2-X-5-Nitroisoquinolinium	(5) $pK_R^+ = -3.70\sigma_X^+ + 11.6$	9	0.982	38
2-(X-Benzyl)-5-nitroisoquinolinium	(6) $pK_R^+ = -3.5\sigma_{CH_2C_6H_4X}^+ + 12.04$ (6a) $pK_R^+ = -1.14\sigma_X + 11.29$	9	0.997	39
1-X-1,8-Naphthyridinium	(7) $pK_R^+ = -4.9\sigma_X^+ + 12.5$	7	0.977	38
1-Cyano-6-X-quinolinium	(8) $pK_R^+ = -6.16\sigma_p - 1.21$	7	0.990	87
1-Cyano-5-X-quinolinium	(9) $pK_R^+ = -6.1(0.2\sigma_p^+ + 0.8\sigma_m^+) - 1.0$ (9a) $pK_R^+ = -5.8(0.5\sigma_p^+ + 0.5\sigma_m^+) - 1.0$	4		87
1-Cyano-7-X-quinolinium	(10) $pK_R^+ = -6.6(0.8\sigma_p + 0.2\sigma_p^+) - 1.1$	4		87
6-X-Benzopyrylium	(11) $pK_R^+ = -5.64\sigma_p - 2.05$	6	0.997	93
7-X-Benzopyrylium	(12) $pK_R^+ = -5.90\sigma_p - 1.82$	4	0.995	93
6-X-Benzothiopyrylium	(13) $pK_R^+ = -5.06\sigma_p + 3.17$	6	0.993	93
7-X-Benzothiopyrylium	(14) $pK_R^+ = -6.09\sigma_p + 3.25$	4	0.999	93
6-X-Isobenzothiopyrylium	(15) $pK_R^+ = -6.93\sigma_p + 2.61$	4	0.996	98
7-X-Isobenzothiopyrylium	(16) $pK_R^+ = -4.88\sigma_p + 2.16$	4	0.975	98
4-(X-Phenyl)-1,3-dithiolium	(17) $pK_R^+ = -1.67\sigma_X + 2.10$	5	0.999	76
2-(X-Phenyl)benzothiopyrylium	(18) $pK_R^+ = -2.70\sigma_X + 5.90$ (18a) $pK_R^+ = -2.25(0.55\sigma_X + 0.45\sigma_X^+) + 5.90$	6	0.990	40
4-(X-Phenyl)benzothiopyrylium	(19) $pK_R^+ = -1.85\sigma_X + 3.58$ (19a) $pK_R^+ = -1.70(0.9\sigma_X + 0.1\sigma_X^+) + 3.58$	9	0.994	40
3-(X-Phenyl)-1,1-dimethyl-2-phenyl-1H-isoindolium	(20) $pK_R^+ = -0.9\sigma_X^+ + 10.4$	4	0.989	121
3-(X-Phenyl)-1,1,2-triphenyl-1H-isoindolium	(21) $pK_R^+ = -1.17\sigma_X^+ + 7.3$	4	0.990	122
3-(X-Phenyl)-1,1-dimethyl-1H-isobenzofurylium	(22) $pK_R^+ = -3.75\sigma_X - 1.52$	12		125

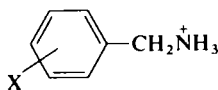
^a Several equations and correlation coefficients have been calculated for the present review from data given in the references indicated.

These relationships are summarized in Table V [Eqs. (3)–(22)] and briefly discussed in the following subsections.

1. Substituents on Ring Nitrogen Atoms

For a number of series of nitrogen heteroaromatic cations, pK_{R+} is well correlated by the Taft σ^* for the substituent on the nitrogen atom [Eqs. (3)–(7); see Table V]. For such correlations ρ^* usually lies in the range 3.5–4.0 (although $\rho^* = 4.9$ for 1,8-naphthyridinium cations³⁸) and is similar to $\rho^* = 3.7$ which has been found¹⁴⁴ for the addition of cyanide ion to C-4 of N-substituted nicotinamide cations. A comparison of Eqs. (5) and (6) is of particular interest. Equation (5) includes a wide range of N-substituents of different structural types in which steric effects may have been expected to play a significant role, whereas Eq. (6) includes only meta- and para-substituted benzyl substituents in which substituent variations are sufficiently removed from the reaction center that substituent effects are purely electronic without any possibility of any significant contribution from steric or solvation factors. The similarity of ρ^* values in Eqs. (5) and (6) indicates that the electronic effects of N-substituents heavily outweigh steric factors in influencing pK_{R+} .

The major factor contributing to the magnitude of ρ^* in these systems is the neutralization of the charged nitrogen atom of the cation upon pseudobase formation. Thus, the values of ρ^* (pK_{R+}) for N-substituted cations are very similar to ρ^* values for the deprotonation of ammonium ions (e.g., $\rho^* = 3.3$ for the acid dissociation constants of tertiary ammonium ions¹⁴⁵). Similarly, the ρ values of Eqs. (4a) and (6a) are similar in magnitude to $\rho = 1.05$ for the acid dissociation of ring-substituted benzylammonium ions (27).¹⁴⁶



(27)

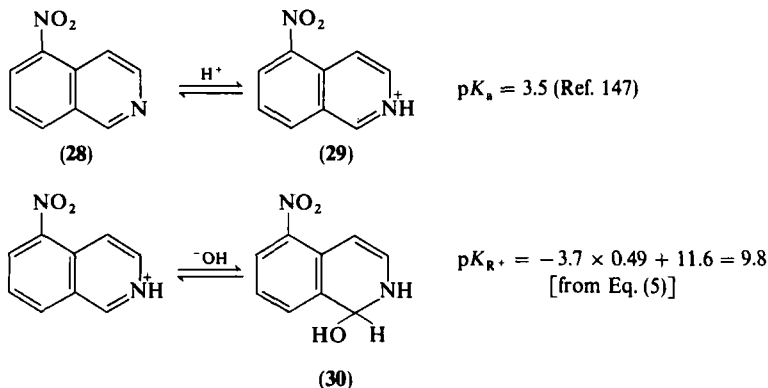
It should be noted that, in principle, correlation equations such as (3)–(7) for the influence of N-substituents on the equilibrium constants for pseudobase formation should allow the estimation of the extent of covalent hydration of the parent nitrogen heterocycle in aqueous solution. Thus using $\sigma^* = 0.49$ for H and the appropriate correlation equation, pK_{R+} for pseudobase formation from the N-protonated parent heterocycle can be estimated.

¹⁴⁴ R. M. Lindquist and E. H. Cordes, *J. Am. Chem. Soc.* **90**, 1269 (1968).

¹⁴⁵ H. K. Hall, *J. Am. Chem. Soc.* **79**, 5441 (1957).

¹⁴⁶ P. R. Wells, "Linear Free Energy Relationships," p. 12. Academic Press, New York, 1968.

This pseudobase is, of course, the covalent hydrate of the neutral parent heterocycle; the relative amounts of covalent hydrate and nonhydrated neutral molecule can then be calculated from the estimated pK_{R+} and the known pK_a value for protonation of the parent heterocycle. As an illustration, the amount of 5-nitroisquinoline present in aqueous solution as its covalent hydrate (30) may be estimated as follows:



$$K_a = 3 \times 10^{-4} = \frac{[H^+][28]}{[29]}$$

$$K_{R+} = 1.6 \times 10^{-10} = \frac{[30][H^+]}{[29]}$$

$$\therefore [30]/[28] = K_{R+}/K_a = 5 \times 10^{-7}$$

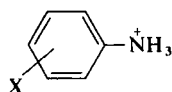
As expected, this ratio of covalent hydrate to nonhydrated species is less than that measured for quinazoline¹⁴² (5.5×10^{-5}).

2. Substituents on Ring Carbon Atoms

Equations (8)–(16) indicate that substituents in the homocyclic ring of quinolinium, benzopyrylium, benzothiopyrylium, and isobenzothiopyrylium cations influence pK_{R+} for pseudobase formation in the heterocyclic ring via ρ values in the range 4.9–6.9. The particular type of σ -constant that has been employed in these correlations is not always readily justifiable theoretically. The use of σ_p (or σ_p^+) for 6-substituents in these classes of cations should be acceptable provided that charge neutralization upon pseudobase formation is the major determinant of the magnitude of ρ . The observed ρ values are considerably larger than $\rho = 2.81$ for the acid dissociation of ring-substituted anilinium ions (31)¹⁴⁸ which can be considered as the simplest

¹⁴⁷ D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," p. 242. Butterworth, London, 1965.

¹⁴⁸ J. Clark and D. D. Perrin, *Q. Rev., Chem. Soc.* **18**, 295 (1964).



(31)

model system for charge neutralization via transmission of substituent effects through the homocyclic ring. The magnitude of ρ (pK_{R+}) in Eqs. (8)–(14) therefore suggests that transmission of substituent effects from the homocyclic ring via C-4 of the heterocyclic ring is also of considerable importance in these systems.

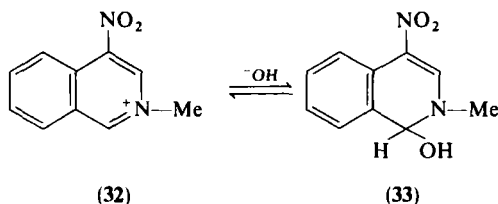
As expected, ρ values for substituents in pendant phenyl rings [Eqs. (17)–(22)] are considerably smaller than for analogous substituents in fused phenyl rings. However, with ρ in the range 0.94–2.70, substituents in pendant phenyl rings can have considerable influence upon the cation–pseudobase equilibrium.

IV. Kinetics and Mechanism of Cation–Pseudobase Equilibration

A. KINETICS

In general, cation–pseudobase equilibration is quite rapid in aqueous solution, and the use of the stopped-flow or temperature-jump techniques is usually required for the measurement of the rates of pseudobase formation from, and decomposition to, the cation. The presence of a large substituent, such as a phenyl ring, at the site of hydroxide ion addition does slow the rate of equilibration sufficiently to allow kinetic measurements by normal spectrophotometric techniques.⁹²

The pH dependence of the pseudo-first-order rate constant k_{obs} for the equilibration of the 2-methyl-4-nitroisoquinolinium cation with its pseudobase (33) is shown in Fig. 3, and is typical of all cation–pseudobase equilibra-



(32)

(33)

tions studied to date. Thus, k_{obs} passes through a minimum value as the pH is varied and becomes linear in $[H^+]$ in acidic solutions and linear in $[OH^-]$ in basic solutions. In certain cases, the minimum in the k_{obs} vs. pH curve may be quite broad rather than sharp as in Fig. 3.³⁹

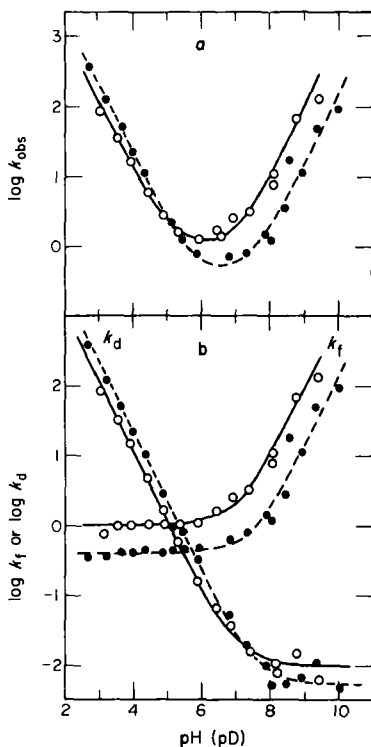


FIG. 3. The pH dependence of (a) k_{obs} , (b) k_f and k_d for the formation and decomposition of the pseudobase of the 2-methyl-4-nitroisoquinolinium cation at 25°. Ionic strength of buffers = 0.1; all rate constants in reciprocal seconds. —○—○— H_2O ; —●—●— D_2O . (From Bunting and Meathrel.⁹²)

In general, k_{obs} is the sum of the individual pseudo-first-order rate constants for formation (k_f) of the pseudobase from, and decomposition (k_d) of the pseudobase species to, the cation. Thus,

$$k_{\text{obs}} = k_f + k_d \quad (23)$$

At equilibrium,

$$k_f[\text{Q}^+] = k_d[\text{QOH}]$$

and hence

$$\frac{k_f}{k_d} = \frac{[\text{QOH}]}{[\text{Q}^+]} = \frac{K_R +}{[\text{H}^+]}$$

Therefore,

$$k_f = k_{\text{obs}} / (1 + [\text{H}^+] / K_R +) \quad (24)$$

and

$$k_d = k_{\text{obs}} / (1 + K_R + / [\text{H}^+]) \quad (25)$$

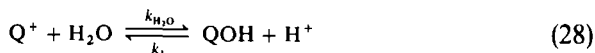
and individual values of k_f and k_d can be calculated from k_{obs} at each pH provided pK_R is known.

The pH dependences of k_f and k_d shown in Fig. 3 for the 2-methyl-4-nitroisquinolinium cation are typical of all simple cation-pseudobase equilibration reactions. The individual pH profiles for k_f and k_d intersect at $pH = pK_R$ where $k_f = k_d$ and the equilibrium solution contains a 1:1 mixture of cation and pseudobase. The pH profiles for k_f and k_d can be fitted by Eqs. (26) and (27), respectively,

$$k_f = k_{OH}[OH^-] + k_{H_2O} \quad (26)$$

$$k_d = k_1[H^+] + k_2 \quad (27)$$

where the rate constants k_{OH} , k_{H_2O} ($=k'_{H_2O} [H_2O]$), k_1 , and k_2 are formally defined by Eqs. (28) and (29).



Thus pseudobase formation occurs via nucleophilic attack of a molecule of water on the cation at low pH or via attack by hydroxide ion in more basic solutions, or the kinetic equivalents of these mechanisms. More detailed consideration of the mechanisms of these reactions is given in Section IV.B.

Literature values for the parameters k_{OH} , k_{H_2O} , k_1 , and k_2 are collected in Table VI^{38,39,46,74,80,86,92,95,109,116,118,119,149,151-167} for a variety of heterocyclic cations. While some of these data have been obtained from direct

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TABLE VI
RATE CONSTANTS FOR CATION-PSEUDOBASE EQUILIBRATION^{a,b}

Cation	k_{OH} ($M^{-1} \text{ sec}^{-1}$)	$k_{\text{H}_2\text{O}}$ (sec^{-1})	k_1 ($M^{-1} \text{ sec}^{-1}$)	k_2 (sec^{-1})	Reference	References to data for substituted cations
$\text{Me}_2\text{C}=\text{NHMe}^+$	1.3×10^6				116	
$\text{Me}_2\text{C}=\text{NHOH}^+$	1.7×10^4				116	
$\text{Me}_2\text{CHCH}=\text{NHMe}^+$	1.3×10^6				116	
5-Anilino-3,4-dihydro-2H-furylium	2.3×10^4	0.0069			149	
1,3-Dimethylimidazolium	4.4×10^{-4c}				151	
1,3-Diphenylimidazolinium	1.6×10^4			250	118, 119	152
3,4-Dimethyloxazolium	8.0×10^{4d}				151	
2-Methyloxazolinium		4.0×10^{-4}			153	
3,5-Dimethylthiazolium	23			0.015	74	151, 154-156
Thiazolinium			0.0085 ^d		157	152, 157
1-(2,4-Dinitrophenyl)-3-carbamoylpyridinium	1.0×10^3				158	158-162
2,4,6-Trimethylpyrylium	1.3×10^4	0.021			80	80
2-Methyl- Δ^2 -thiazinium	13	1.0×10^{-6}			152	
2,3-Dimethylbenzoxazolium	1.6×10^5	0.00347			163	163
3-Methylbenzothiazolium	1.6×10^4				156	
1-Benzyl-5-nitroquinolinium	1.01×10^5	0.0031	5.7×10^8	183	39	39

1-Methyl-3-nitroquinolinium	1.3×10^5	0.43	2.8×10^6	0.0071	86	
1-Methyl-5,7-dinitroquinolinium	2.2×10^6	0.27	7.2×10^7	6.4	39	
2-Methyl-4-nitroisoquinolinium	8.8×10^6	1.04	1.33×10^5	0.011	92 ^e	38, 39
<i>f</i>		0.047 ^g	2.6 ^g		95	
1,5-Dimethyl-1,5-naphthyridinium	7.6×10^7	22	2.9×10^6	0.097	39	
158	4.6×10^6	56			164	
65	1.5×10^6				165	
10-Methylacridinium	550	0.0024	2.4×10^7	0.058	92 ^e	166
9-Phenyl-10-methylacridinium	1.3	5.3×10^{-6}	5.7×10^5	0.0014	92 ^e	
37	1.3×10^4			1.4	109	
17	5.5×10^5	0.059	2.6×10^8	25	46	
18	9.4×10^5	0.12	1.9×10^8	14	46	
Pyrazino[1,2,3,4- <i>lmn</i>]-1,10-phenanthroline	1.5×10^6	0.115	1.9×10^5	0.032	46	

^a In water at 20°–25° unless otherwise indicated.

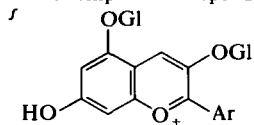
^b See Bunting and Perrin¹⁶⁷ for $k_{\text{H}_2\text{O}}$ for a variety of substituted quinazolinium cations.

^c In 53% dimethyl sulfoxide–47% water at 40°.

^d At 30°.

^e Also temperature dependence (15°–55°) of each rate constant.

f



Ar = 3,5-(CH₃O)₂-4-HOC₆H₂.

^g At 4°.

studies of cation–pseudobase equilibration, in certain cases only one of these four rate constants is available. In such cases, this rate constant has usually been obtained from a kinetic analysis of a more complicated multistep reaction that involves pseudobase formation from the cation as the initial step. Values for pK_{R+} are usually unavailable in these latter cases.

It is clear from perusal of the data in Table VI that there is no overall general correlation between pK_{R+} and k_{OH} or k_{H_2O} ; e.g., although the 2-benzyl-5-nitroquinolinium and 9-phenyl-10-methylacridinium cations have similar pK_{R+} values, the values of k_{OH} for these two cations differ by a factor of 10^5 . However, within series of very closely structurally related cations, useful linear rate–equilibrium correlations do exist.³⁹ Thus, Fig. 4 displays linear relationships between $\log k_{OH}$ and pK_{R+} for quinolinium and isoquinolinium cations. The correlation lines in this figure are given by Eqs. (30) and (31). These correlations cover six units of the pK_{R+} scale and a

$$\text{Quinolinium cations: } \log k_{OH} = -0.45pK_{R+} + 10.03 \quad (30)$$

$$\text{Isoquinolinium cations: } \log k_{OH} = -0.36pK_{R+} + 8.84 \quad (31)$$

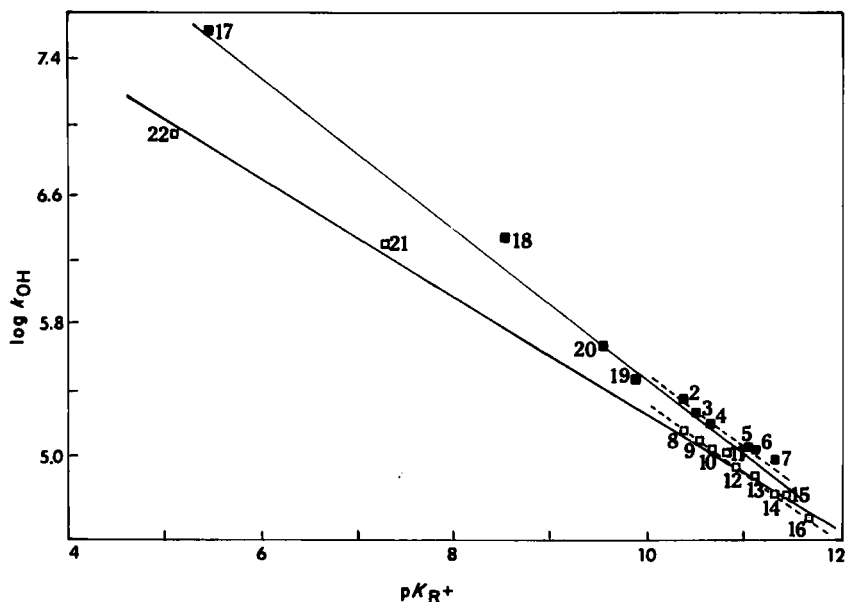


FIG. 4. Relationship between $\log k_{OH}$ and pK_{R+} for quinolinium (■) and isoquinolinium (□) cations. Cations are identified by numbers in Bunting and Norris³⁸. Full lines correspond to Eqs. (30) and (31). (Reprinted with permission from Bunting and Norris,³⁹ *J. Am. Chem. Soc.* **99**, 1189 (1977). Copyright by the American Chemical Society.)

variety of substitution patterns in the quinolinium and isoquinolinium ring systems as well as various N-substituents. The correlation line for quinolinium cations includes the 1,5-dimethylnaphthylridinium dication and the two bridged phenanthroline dications **17** and **18**, so that a broad general applicability of these correlations is apparent. On the other hand, it is clear that different correlation lines are required for quinolinium and isoquinolinium cations. Differences in solvation patterns in the vicinity of the site of hydroxide ion addition would seem to explain most simply the need for different correlation lines for these two series of cations. There do not appear to be sufficient data available at present to allow the construction of similar rate-equilibrium correlations for other classes of cations. Further systematic studies of the influence of cation structure and of substituent effects on the rates and equilibria of pseudobase formation are required to further the quantitative understanding of cation-pseudobase equilibration.

An interesting feature of the kinetic data in Table VI is the relative insensitivity of the $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ ratio to substituent effects within a series of structurally related cations. Thus, for quinolinium and isoquinolinium cations, $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ is within a factor of 2 of $2 \times 10^7 \text{ M}^{-1}$ for at least a 100-fold variation in each of k_{OH} and $k_{\text{H}_2\text{O}}$. Similarly, $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ is the same within experimental error ($2.4 \times 10^5 \text{ M}^{-1}$) for the 10-methylacridinium cation and its 9-phenyl derivative despite a major structural variation at the site of nucleophilic attack and a resulting 400-fold difference in k_{OH} for these two cations.

From the following analysis,³⁹ it is apparent that the establishment of a linear $\log k_{\text{OH}}$ vs. $\text{p}K_{\text{R}^+}$ correlation and an approximately constant $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ ratio for a series of cations allows the complete kinetic description of cation-pseudobase equilibration of any other member of the series for which $\text{p}K_{\text{R}^+}$ is available. The observed pseudo-first-order rate constant for cation-pseudobase equilibration can be expressed using Eqs. (26) and (27) as

$$k_{\text{obs}} = k_1[\text{H}^+] + k_2 + k_{\text{OH}}K_{\text{w}}/[\text{H}^+] + k_{\text{H}_2\text{O}} \quad (32)$$

in which K_{w} is the autoprotolysis constant of water. Differentiation of k_{obs} with respect to $[\text{H}^+]$ gives

$$d(k_{\text{obs}})/d[\text{H}^+] = k_1 - k_{\text{OH}}K_{\text{w}}/[\text{H}^+]^2$$

The observed pH-rate profile (e.g., Fig. 3) will pass through a minimum value when this derivative is zero, i.e., at

$$[\text{H}^+]_{\text{min}} = (k_{\text{OH}}K_{\text{w}}/k_1)^{1/2}$$

Using this relationship and Eq. (32), the minimum value of k_{obs} will be

$$k_{\text{obs}}^{\text{min}} = k_2 + k_{\text{H}_2\text{O}} + 2(k_1k_{\text{OH}}K_{\text{w}})^{1/2} \quad (33)$$

Now,

$$k_2 = k_{\text{OH}}K_w/K_{\text{R}^+} \quad (34)$$

and

$$k_{\text{H}_2\text{O}} = k_1 K_{\text{R}^+} \quad (35)$$

so that, for $k_{\text{OH}}/k_{\text{H}_2\text{O}} = 10^7$, which appears to be typical of many hetero-aromatic cations, Eq. (35) may be rearranged to

$$k_1 = 10^{-7} k_{\text{OH}}/K_{\text{R}^+}$$

Thus,

$$[\text{H}^+]_{\text{min}} = (10^7 K_w K_{\text{R}^+})^{1/2}$$

and

$$\text{pH}_{\text{min}} = 3.5 + 0.5 \text{p}K_{\text{R}^+} \text{ at } 25^\circ, \text{ when } K_w = 10^{-14}$$

Equation (33) becomes

$$\begin{aligned} k_{\text{obs}}^{\text{min}} &= k_{\text{OH}}K_w/K_{\text{R}^+} + 10^{-7}k_{\text{OH}} + 2k_{\text{OH}}(10^{-7}K_w/K_{\text{R}^+})^{1/2} \\ &= k_{\text{OH}}[10^{-14}/K_{\text{R}^+} + 10^{-7} + 6.3 \times 10^{-11}/(K_{\text{R}^+})^{1/2}] \end{aligned} \quad (36)$$

while Eq. (32) becomes

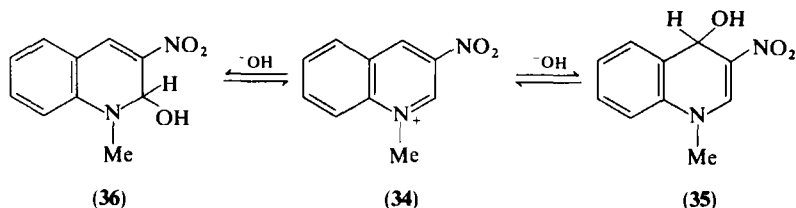
$$k_{\text{obs}} = k_{\text{OH}}[(10^{-7}[\text{H}^+] + 10^{-14})/K_{\text{R}^+} + [\text{OH}^-] + 10^{-7}] \quad (37)$$

Clearly, substitution of Eq. (30) or (31) into (36) and (37) gives k_{obs} and $k_{\text{obs}}^{\text{min}}$ as a function of K_{R^+} alone. Thus, the measurement of $\text{p}K_{\text{R}^+}$ allows calculation of the complete pH profile, provided Eq. (30) or (31) is applicable and with the only other assumption being that $k_{\text{OH}}/k_{\text{H}_2\text{O}} = 10^7$. In general, of course, one would prefer independently to determine the pH-rate profile from kinetic measurements; however, the preceding expressions for k_{obs} , $k_{\text{obs}}^{\text{min}}$, and pH_{min} in terms of K_{R^+} allow a useful preliminary determination of the pH region that is likely to be amenable to investigation by the stopped-flow technique.

Clearly, these derivations can be modified for other systems in which $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ takes values other than 10^7 .

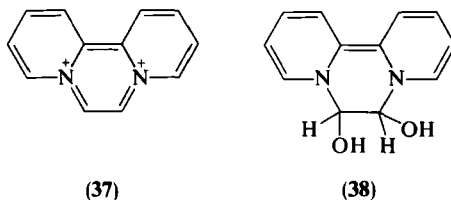
The description of the kinetics of cation-pseudobase equilibration by Eqs. (26) and (27) seems to be sufficiently general that deviations from these kinetic equations may be used to diagnose kinetic complexities in these reactions. Thus, the pH independence of k_t at high pH in pseudobase formation from the 1-methyl-3-nitroquinolinium cation has been shown to arise from the preference for different kinetically and thermodynamically controlled pseudobase products from this cation.⁸⁶ A detailed kinetic and

spectroscopic study has established that the C-4 adduct **35** ($pK_{R+} = 6.82$) is the predominant pseudobase species present in aqueous solution at equilibrium. However, hydroxide ion attack at C-2 to give **36** occurs much



faster than at C-4, and by use of the stopped-flow technique $pK_{R+} = 9.16$ has been obtained for the formation of this kinetically controlled pseudobase. The pH-independent k_f for this cation in basic solution actually represents the isomerization of **36** to the thermodynamically more stable **35**.

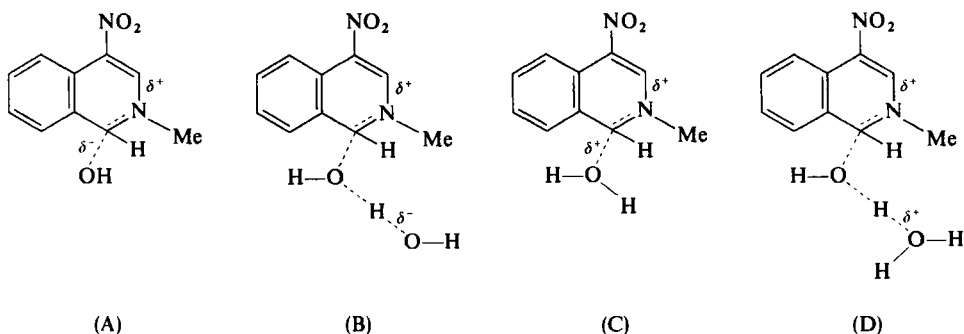
The complicated nature of the rapid spectral changes which occur in basic solutions of the dication **37** have been interpreted¹⁰⁹ in terms of the



formation of a monopseudobase by hydroxide ion addition at C-2 or C-4 of one of the pyridinium rings, and a dipseudobase **38** at higher pH by the addition of two hydroxide ions in the pyrazinium ring of **37**.

B. MECHANISM

The empirical equations (26) and (27) suggest that two kinetically distinguishable pathways are available for each of pseudobase formation and decomposition in aqueous solution.⁹² The pH-independent term k_{H_2O} for pseudobase formation is interpretable either as a rate-determining attack of a water molecule on the heterocyclic cation followed by a rapid deprotonation (transition state C) or alternatively as the general-base-catalyzed attack (by another water molecule) of a molecule of water on the heterocyclic cation (transition state D). In more basic solutions, this mechanism becomes unimportant compared with the direct attack of hydroxide ion ($k_{OH}[OH^-]$) on the heterocyclic cation (transition state A), or alternatively the kinetically



equivalent hydroxide-ion-catalyzed attack (as a general base) of a water molecule on the cation (transition state B).

The mechanistic significance of the terms in Eq. (27) for pseudobase decomposition must, of course, be the microscopic reverse of the interpretations given for the pseudobase formation reactions. Thus, $k_1[\text{H}^+]$ is the microscopic reverse of the $k_{\text{H}_2\text{O}}$ term, and may be formally interpreted as either the spontaneous loss of a molecule of water from the O-protonated pseudobase (i.e., specific-acid catalysis; transition state C) or alternatively as elimination of hydroxide ion from the neutral pseudobase molecule with the aid of H_3O^+ as a general-acid catalyst (transition state D). The k_2 term is the microscopic reverse of $k_{\text{OH}}[\text{OH}^-]$, and so formally represents either the spontaneous decomposition of the pseudobase to heterocyclic cation and hydroxide ion (transition state A) or the kinetically equivalent general-acid catalysis of this reaction by a water molecule (transition state B).

Detailed studies of the temperature dependence of the kinetics of cation-pseudobase equilibration have been reported⁹² for three cations, and activation parameters have been evaluated for each of k_{OH} , $k_{\text{H}_2\text{O}}$, k_1 , and k_2 in these cases. Whereas entropies of pseudobase formation from the cation are positive (Section III), the entropies of activation associated with k_{OH} are quite negative (-11 to -17 cal mol⁻¹ deg⁻¹). For direct hydroxide ion attack on the cation via transition state A, one would predict an entropy of activation similar to the entropy of formation of the pseudobase from heterocyclic cation and hydroxide ion. Interpretation of k_{OH} in terms of transition state B in which hydroxide ion acts as a general-base catalyst for the attack of a water molecule seems to be more consistent with the observed entropies of activation. The k_2 step, which is the microscopic reverse of k_{OH} , would then be interpreted as general-acid-catalyzed (by a water molecule) decomposition of the neutral pseudobase to the cation. These interpretations of k_{OH} and k_2 are also consistent with the observed solvent isotope effects for the reactions in H_2O and D_2O and with the presence of general

acid-base catalysis by buffer components.⁹² Transition state B is also consistent with Ritchie's postulate¹⁶⁸ that the transition state for a cation-anion combination reaction involves considerable separation of the cation and anion and is probably somewhat similar to an ion pair separated by one solvent molecule. The $k_{\text{H}_2\text{O}}$ and k_1 terms also are probably associated with transition state D in which $k_{\text{H}_2\text{O}}$ reflects the nucleophilic attack of one water molecule assisted by general-base catalysis from a second water molecule and k_1 represents general-acid catalysis by H_3O^+ of pseudobase decomposition.

Catalysis of cation-pseudobase equilibration has been observed by a number of buffer species.⁹² This catalysis appears to be reasonably complex, and a more detailed study than is available to date will be required to allow a complete description of the catalytic steps involved. In general, it is found⁹² that the effects of buffer catalysis tend to be leveled out by working at constant buffer ionic strength (e.g., $I = 0.1$).

V. Reactions of Pseudobases in Aqueous Solution

A. RING-OPENING TAUTOMERISM

The problem of ring-chain tautomerism between pseudobase carbinolamines and their amino-carbonyl isomers has been a central question in studies of pseudobase structure. Much of the early work on alkaloidal heterocyclic cations was devoted to attempts to distinguish between the pseudobase and its ring-opened tautomer on the basis of chemical reactivity. This area forms a major part of Beke's review.⁴ In general, experiments designed on the basis of expected differences in the chemical reactivity of the carbinolamine and amino-carbonyl tautomers do not give unambiguous information regarding the major component of this tautomeric mixture. A negative test in the presence of typical carbonyl-specific reagents can usually be interpreted in terms of little of the ring-opened species being present. However, a positive test in such experiments does not distinguish between the ring-opened species being the major tautomer or the reaction proceeding via the minor component of a facile tautomeric equilibrium.

Spectroscopic techniques which do not influence the position of the equilibrium can more certainly be used to ascertain the composition of the equilibrium tautomeric mixture. The presence of significant amounts of

¹⁶⁸ C. D. Ritchie, *Acc. Chem. Res.* **5**, 348 (1972).

the ring-opened carbonyl tautomer is usually readily detectable in the solid state and in solution in many organic solvents by IR and/or PMR spectroscopies. Habermehl *et al.*¹⁶⁹ have claimed distinctive mass spectra for isomeric quaternary hydroxides, carbinolamines, and amino-aldehydes in the berberine series of alkaloidal isoquinolinium cations. However, it seems unlikely that mass spectrometric analyses would reflect normal equilibrium tautomeric ratios in solution. It must be realized that the ring-opened tautomer will *always* be present to some extent at equilibrium in carbinolamine pseudobases and related species in the solid state and in solution. Spectroscopic techniques will usually definitively indicate whether one of the tautomers predominates or whether the equilibrium mixture contains significant amounts (say, >5%) of each isomer. In the latter case, the composition of the tautomeric mixture may be ascertainable spectroscopically. Since this composition will be solvent-dependent and substituent-dependent, considerable caution must be exercised in extrapolation of data to other solvents or to related pseudobase molecules.

Hammond,¹⁷⁰ Jones,¹⁷¹ and most recently Escale and Verducci¹⁷² have reviewed ring-chain tautomerism in general terms, and have summarized the many factors which influence the position of this equilibrium. Briefly, these factors include molecular properties such as size and degree of saturation of the ring, and electronic and steric effects of substituents, plus environmental factors such as temperature, solvent, etc. No attempt will be made here to consider these effects in detail, although many of the systems that have been studied can be considered to be pseudobases (e.g., carbinolamines) of relatively unstable heterocyclic cations. The work of Alper *et al.*,¹⁷³⁻¹⁷⁶ Lamon *et al.*,¹⁷⁷ Singh and Singh,¹⁷⁸ and Toth *et al.*¹⁷⁹ represents just a few of many examples of investigation in this area.

In Section II, a strategy was described for the investigation of the ring opening of pseudobases in aqueous solutions on the basis of a comparison of the electronic absorption spectra of the pseudobases formed by a particular heterocyclic cation in aqueous and alcoholic solutions. Similar

¹⁶⁹ G. Habermehl, J. Schunck, and G. Schaden, *Justus Liebigs Ann. Chem.* **742**, 138 (1970).

¹⁷⁰ G. Hammond, in "Steric Effects in Organic Chemistry" (M.S. Newman, ed.), p. 460. Wiley, New York, 1956.

¹⁷¹ P. R. Jones, *Chem. Rev.* **63**, 461 (1963).

¹⁷² R. Escale and J. Verducci, *Bull. Soc. Chim. Fr.* p. 1203 (1974).

¹⁷³ A. E. Alper and A. Taurins, *Can. J. Chem.* **45**, 2903 (1967).

¹⁷⁴ H. Alper, *J. Chem. Soc. D* p. 383 (1970).

¹⁷⁵ H. Alper and A. E. Alper, *J. Org. Chem.* **35**, 835 (1970).

¹⁷⁶ H. Alper, E. C. Keung, and R. A. Partis, *J. Org. Chem.* **36**, 1352 (1971).

¹⁷⁷ R. W. Lamon, W. J. Humphlett, and W. P. Blum, *J. Heterocycl. Chem.* **4**, 349 (1967).

¹⁷⁸ H. Singh and S. Singh, *Tetrahedron Lett.* p. 585 (1970).

¹⁷⁹ G. Toth, G. Hornyak, and K. Lempert, *Chem. Ber.* **110**, 1492 (1975).

pseudobase spectra in these two media clearly indicate the presence of the ring-closed hydroxy tautomer as the major tautomeric component in aqueous solution. Care should be taken, of course, to identify the alkoxide adduct (usually by PMR spectroscopy) as the major species present in basic alcoholic solutions of the heterocyclic cation. Spectroscopic studies of authentic alkoxide adducts of a cation have been used on a number of occasions to show that the simple pseudobase is not the major species present in aqueous solutions of that cation.^{55,67,180-186}

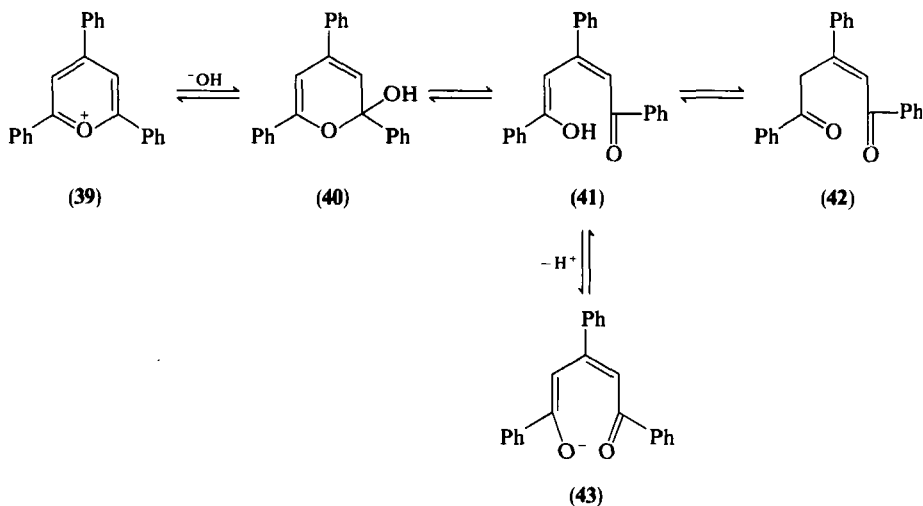
There are numerous reports in the literature¹⁸⁷⁻¹⁹³ of the isolation of the ring-opened tautomer of a pseudobase upon treatment of an aqueous solution of a heterocyclic cation with base. However, it is usually unclear whether the isolated product accurately reflects the predominant equilibrium solution tautomer or is simply the less soluble species of the tautomeric pair.

The following sections will emphasize those systems in which reasonable attempts have been made to conduct detailed investigations of ring-opening reactions of pseudobases in aqueous solution. In addition, there are numerous reactions of heterocyclic molecules, under a wide variety of reaction conditions, which have been postulated to proceed via ring-opening of a pseudobase intermediate.^{100,194-203}

- ¹⁸⁰ A. Belly, C. Petrus, and F. Petrus, *Bull. Soc. Chim. Fr.* p. 1025 (1974).
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¹⁸² I. Degani, R. Fochi, and P. Tundo, *J. Heterocycl. Chem.* **11**, 507 (1974).
¹⁸³ B. J. Huckings and M. D. Johnson, *J. Chem. Soc. B* p. 63 (1966).
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¹⁸⁶ J. Metzger, H. Larivé, R. Dennilaule, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.* p. 2879 (1964).
¹⁸⁷ K. Arakawa, T. Miyasaka, and K. Satoh, *Chem. Pharm. Bull.* **25**, 299 (1977).
¹⁸⁸ H. G. O. Becker and H. Böttcher, *Tetrahedron* **24**, 2687 (1968).
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¹⁹¹ E. C. Campbell, E. E. Glover, and G. Trenholm, *J. Chem. Soc. C* p. 1987 (1969).
¹⁹² J. Elliot, *J. Org. Chem.* **29**, 305 (1964).
¹⁹³ H. Pauls and F. Krohnke, *Chem. Ber* **109**, 3646 (1976).
¹⁹⁴ A. Albert and H. Yamamoto, *J. Chem. Soc. B* p. 956 (1966).
¹⁹⁵ J. Clark, B. Parvizi, and I. W. Southon, *J. Chem. Soc., Perkin Trans. 1* p. 125 (1976).
¹⁹⁶ D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.* p. 5062 (1960).
¹⁹⁷ A. Fozard, L. D. Davies, and C. K. Bradsher, *J. Chem. Soc. C* p. 3650 (1971).
¹⁹⁸ F. Linhart and S. Hunig, *Chem. Ber.* **104**, 913 (1971).
¹⁹⁹ J. Lee and W. W. Paudler, *Chem. Commun.* p. 1636 (1971).
²⁰⁰ D. D. Perrin and I. H. Pitman, *J. Chem. Soc.* p. 7071 (1965).
²⁰¹ H. Singh, S. Singh, and K. B. Lal, *Chem. Ind. (London)* p. 255 (1972).
²⁰² M. Shamma and L. Toke, *J. Chem. Soc., Chem. Commun.* p. 740 (1973).
²⁰³ R. S. Shadbolt, *J. Chem. Soc. C* p. 1669 (1971).

1. Perylium, Thiopyrylium, and Related Cations

Pyrylium cations have long been known to undergo ring-opening reactions in aqueous solution.^{80,204-214} Berson²⁰⁴ showed that the electronic spectral properties of the 2,4,6-triphenylpyrylium cation (**39**) in neutral aqueous solution are consistent with the predominance of the diketo tautomer **42** rather than that of the ketohydroxy tautomer **41**. There has been a tendency in the literature to refer to **41** or **42** as the pseudobase of **39**.



However, it seems more reasonable to reserve this name for the true nucleophilic adduct **40** and to refer to **41** and **42** as ring-opened tautomers of this pseudobase. More basic aqueous solutions of this cation are orange-pink ($\lambda_{\max} = 490$ nm), and this is ascribed^{204,210,214} to the presence of the enolate anion **43** derived from **41** or **42**. Griot *et al.*²⁰⁷ claim the isolation of the true pseudobase **40** from highly basic solutions.

²⁰⁴ J. A. Berson, *J. Am. Chem. Soc.* **74**, 358 (1952).

²⁰⁵ J. J. Basselier, *Ann. Chim. (Paris)* [13] **6**, 1131 (1961).

²⁰⁶ W. Diltthey and T. Bottler, *Chem. Ber.* **52**, 2040 (1919).

²⁰⁷ J. P. Griot, J. Royer, and J. Dreux, *Tetrahedron Lett.* p. 2195 (1969).

²⁰⁸ R. Hubaut and J. Landais, *Hebd. Services Acad. Sci.* **278**, 1247 (1974).

²⁰⁹ R. Lombard and J. P. Stephan, *Bull. Soc. Chim. Fr.* p. 1458 (1958).

²¹⁰ R. Lombard and A. Kress, *Bull. Soc. Chim. Fr.* p. 1528 (1960).

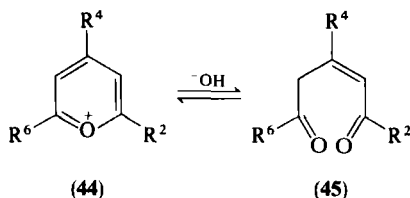
²¹¹ C. L. Pedersen, *Acta Chem. Scand. Ser. B* **29**, 791 (1975).

²¹² G. Rio and Y. Fellion, *Tetrahedron Lett.* p. 1213 (1962).

²¹³ G. Salvadori and A. Williams, *J. Am. Chem. Soc.* **93**, 2727 (1971).

²¹⁴ R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 207 and 217 (1956).

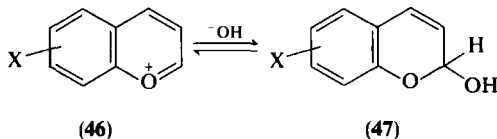
Williams⁸⁰ has studied the pH dependence of the rate of ring opening for several trisubstituted pyrylium cations (**44**) in the region pH = 3–10.



The equilibrium $44 \rightleftharpoons 45$ is defined by an apparent ionization constant $K'_a = [\text{H}^+][45]/[44]$, which is related to pK_{R^+} for **44** and the equilibrium constant K_{eq} ($[45]/[\text{QOH}]$) for pseudobase–diketone equilibration by $K'_a = K_{R^+} \times K_{eq}$ (for convenience, the presence of small amounts of the ketohydroxy tautomer is neglected). The rate of ring opening is found to depend on an ionization constant denoted by Williams as K_a , but which most probably is actually K_{R^+} for cation–pseudobase equilibration. On the basis of this assumption, the following values of K_{eq} can be calculated: >500 (**44**; $\text{R}^2 = \text{R}^4 = \text{R}^6 = \text{Me}$); 63(**44**; $\text{R}^2 = \text{Me}$, $\text{R}^4 = \text{R}^6 = \text{Ph}$); 50(**44**; $\text{R}^2 = \text{R}^4 = \text{R}^6 = \text{Ph}$). The observed general-base catalysis of this reaction is ascribable to the catalysis of a slow ring-opening reaction following rapid pseudobase formation. In a related kinetic study, Salvadori and Williams²¹³ have shown that the 2,6-dimethyl-4-ethoxypyrylium cation undergoes a similar ring-opening equilibration for pH > 5 , but in more acidic solutions 2,6-dimethyl-4-pyrone is the predominant product.

Hubaut and Landais²⁰⁸ have studied the kinetics of diketone–cation equilibration in the region pH = 0–5 in 66% aqueous alcohol. They interpret their data in terms of an acid-catalyzed enolization which is the rate-determining step for the ring-closing reaction in these solutions.

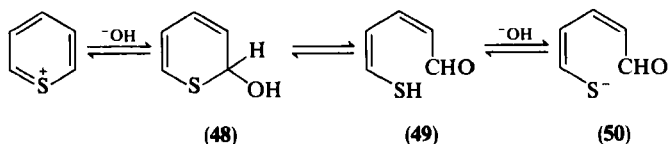
In a spectral study of aqueous solutions of a series of benzopyrylium cations **46**, Canalini *et al.*⁹³ were able to detect significant ring opening of



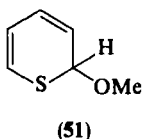
the pseudobases **47** in only one case—the 7-methoxy derivative. This stabilization of the pseudobase relative to its ring-opened tautomer by a fused ring is quite consistent with entropic considerations.

Degani *et al.*¹⁸¹ have studied aqueous solutions of the thiopyrylium cation. Electronic spectral data indicate the presence of the ring-opened

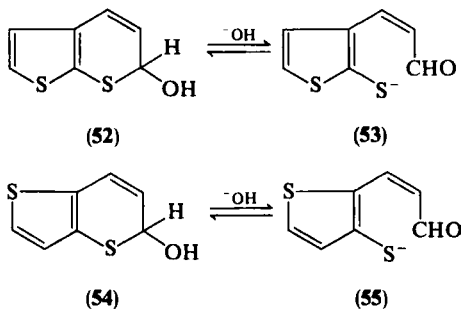
tautomer **49** of the pseudobase **48** in neutral solution, while the anion **50** was detected by PMR spectroscopy in solutions of pH > 11. PMR spectral evidence for the presence of the methoxide adduct **51** is presented for basic



methanolic solutions of this cation. These workers also report⁸⁴ that the pseudobases **52** and **54** undergo a relatively slow ring opening in basic



aqueous solutions to generate the anions **53** and **55**, respectively.

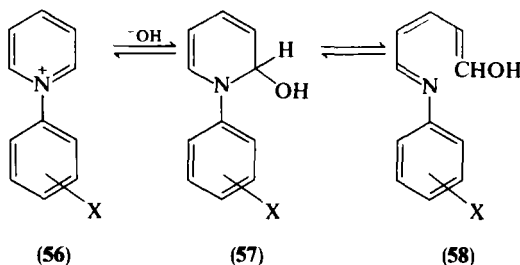


2. Pyridinium and Related Cations

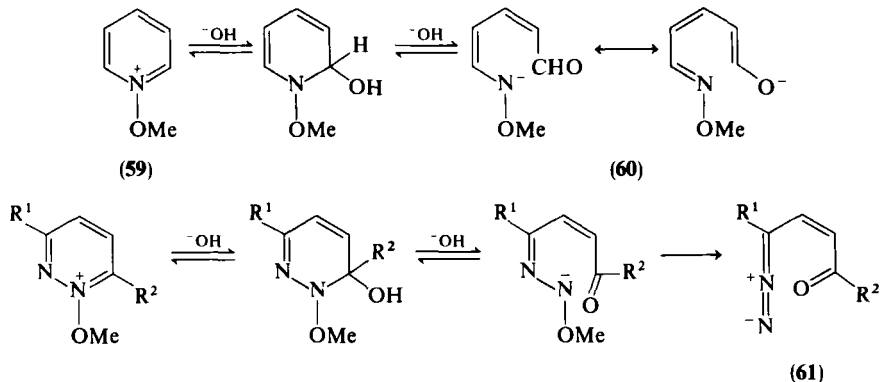
Many pyridinium cations have been observed to undergo ring-opening reactions in aqueous base. Unlike pyrylium ions, pyridinium ions usually require quite basic solutions for ring opening to occur, and the reactions are rarely reversible due to the intervention of degradation reactions of the ring-opened product. This requirement for quite basic conditions is a reflection of the difficulty of pseudobase formation in pyridinium cations, and the different pH requirements for ring opening of pyridinium and pyrylium cations are directly related to the relative susceptibilities of these cations to pseudobase formation (Table IV).

The products of the ring opening of pyridinium cations in aqueous base are usually glutacanaldehyde derivatives. Early work in this area has been

reviewed.²¹⁵ More recently, reports of the ring opening of the 1-methyl-3-cyanopyridinium cation in aqueous base have come from three separate laboratories,^{61,216,217} however, the isolated products from these reactions seem to be very sensitive to the exact experimental conditions employed. Kavalek *et al.*²¹⁸ have investigated the kinetics of the conversion of *N*-phenylpyridinium cations (**56**) to the corresponding anils (**58**) of glutaconaldehyde in basic 50–90% aqueous methanol.



Several reports^{219–222} have appeared on the ring opening of *N*-alkoxy-pyridinium cations in aqueous base (e.g., **59** \rightarrow **60**), and Katritzky *et al.*^{219,220} have investigated the kinetics of these reactions. *N*-Methoxypyridazinium cations undergo similar reactions, with the ultimate products being vinyl-diazoalkanes (**61**).²²³



²¹⁵ E. N. Shaw, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part II, p. 58. Wiley (Interscience), New York, 1962.

²¹⁶ J. H. Blanch and K. Fretheim, *J. Chem. Soc. C* p. 1892 (1971).

²¹⁷ F. M. Moracci, A. Casini, F. Liberatore, and V. Carelli, *Tetrahedron Lett.* p. 3723 (1976).

²¹⁸ J. Kaválek, J. Polanský, and V. Štěrbá, *Collect. Czech. Chem. Commun.* **39**, 1049 (1974).

²¹⁹ R. Eisenthal and A. R. Katritzky, *Tetrahedron* **21**, 2205 (1965).

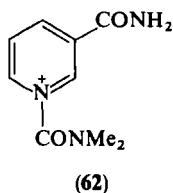
²²⁰ A. R. Katritzky and E. Lunt, *Tetrahedron* **25**, 4291 (1969).

²²¹ J. Schnekenburger and D. Heber, *Tetrahedron* **30**, 4055 (1974).

²²² J. Schnekenburger and D. Heber, *Chem. Ber.* **107**, 3408 (1974).

²²³ T. Tsuchiya, C. Kaneko, and H. Igeta, *J. Chem. Soc., Chem. Commun.* p. 528 (1975).

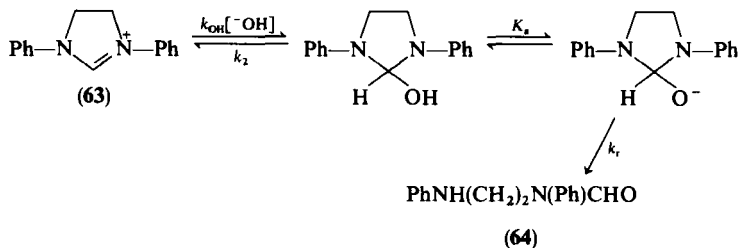
Johnson and co-workers^{159,161,162,224,225} have made detailed kinetic studies of the ring-opening reactions of nicotinamide cations in aqueous base with particular emphasis on the *N*-(*N,N*-dimethylcarbamoyl) derivative (**62**) and nicotinamide adenine dinucleotide.



The pseudobases from quinolinium and isoquinolinium cations are much less susceptible to ring opening than are their pyridinium analogs. Recent examples in which the ring-opened species have been characterized beyond doubt are confined to strongly electron-withdrawing substituents on the ring nitrogen atom.^{88,192,226,227}

3. Imidazolinium and Related Cations

Robinson and Jencks^{118,119,165,228} have made detailed kinetic studies of the hydrolysis of several imidazolinium cation derivatives. With the aid of stopped-flow studies, all rate and equilibrium constants shown have been evaluated^{118,119,228} at 25° for the ring opening of the 1,3-diphenylimidazolinium cation (**63**) in aqueous base to *N*-(2-anilinoethyl) formanilide (**64**). Kinetic studies¹⁶⁵ of the hydrolysis of the *N*^{5,10}-methenyltetrahydrofolate



cation **65** to *N*¹⁰-formyltetrahydrofolic acid (**67**) indicate that the formation of the pseudobase **66** from the cation is general-base catalyzed, whereas the ring-opening reaction of **66** is subject both to general-acid and to general-

²²⁴ S. L. Johnson and K. Rumon, *Tetrahedron Lett.* p. 1721 (1966).

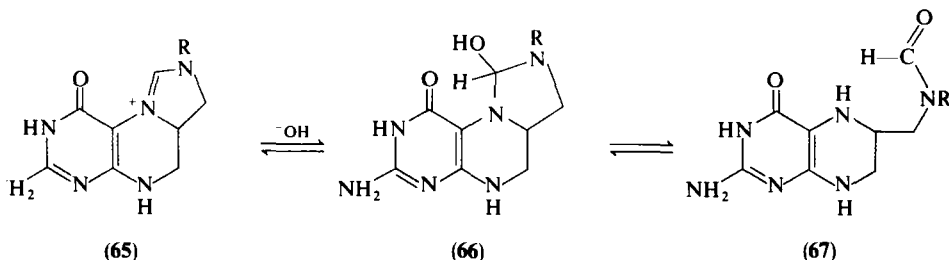
²²⁵ C. C. Guilbert and S. L. Johnson, *Biochemistry* **10**, 2313 (1970).

²²⁶ D. Beke and C. Szantay, *Justus Liebigs Ann. Chem.* **640**, 127 (1961).

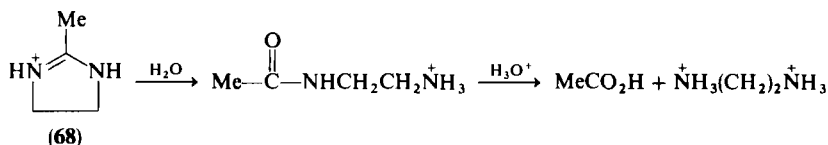
²²⁷ R. Hull, *J. Chem. Soc. C* p. 1777 (1968).

²²⁸ D. R. Robinson and W. P. Jencks, *J. Am. Chem. Soc.* **89**, 7088 (1967).

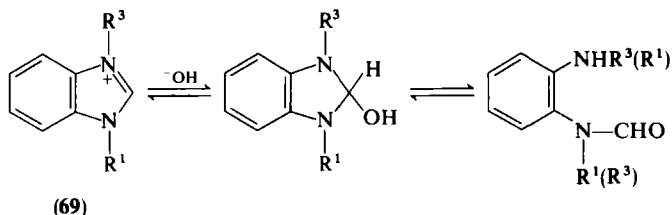
base catalysis. Either step may be rate-determining, depending upon the concentrations of catalytic buffer species. A detailed analysis for the case of catalysis by imidazole has been presented.¹⁶⁵



Haake and Watson²²⁹ report a kinetic study of the hydrolysis of the 2-methyl-2-imidazolium cation **68** in strongly acidic solutions.



Duclos and Haake¹⁵¹ report the 1,3-dimethylimidazolium cation to be stable in quite basic aqueous solutions but have measured the rate of ring opening of this cation in a strongly basic dimethyl sulfoxide–water mixture. There are many reports in the literature^{189,230–232} of the ready ring opening of the pseudobases of benzimidazolium cations (69), but in all cases the evidence seems to rest on the structure of a product isolated from basic solutions of these cations. There is at least one report²³³ of the isolation



²²⁹ P. Haake and J. W. Watson, *J. Org. Chem.* **35**, 4063 (1970).

²³⁰ J. Bourson, *Bull. Soc. Chim. Fr.* p. 3541 (1971).

²³¹ O. Gerngross, *Chem. Ber.* **46**, 1913 (1913).

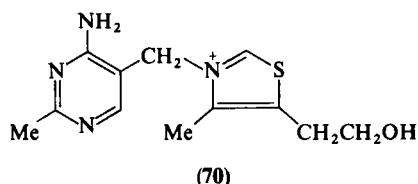
²³² K. J. Morgan and A. M. Turner, *Tetrahedron* **22**, 1175 (1966).

²³³ A. Patchornik, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.* **79**, 6416 (1957).

of the pseudobase in this system; however, the tautomerism of the pseudobases of these cations in solution does not seem to have been investigated.

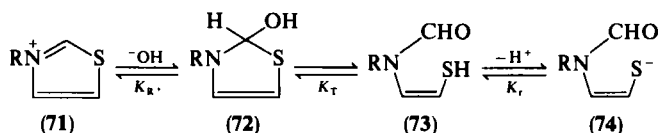
4. Thiazolium and Related Cations

There has been considerable interest in the reactions of thiazolium cations in aqueous solutions. Most of this interest has been generated by the desire to understand the chemistry of the biologically important thiazolium cation, thiamine (vitamin B₁) (70).



Titration of a neutral aqueous solution of thiamine with standard base produces a one-step titration curve that corresponds to two equivalents of base per mole of thiamine cation.^{73,156,234-237} The midpoint of this titration curve occurs in the vicinity of pH 9.3 at 25° and is usually designated as pK_{av} . Other thiazolium and benzothiazolium cations show similar two-equivalent titration steps, and values for pK_{av} for a variety of such cations have been measured. Values of pK_{av} in the range 9.3–11.2 have been reported^{73,74,155,156,234} for various thiazolium cations.

Basic aqueous solutions of a thiazolium cation contain the ring-opened thiolate anion 74 derived from the pseudobase 72. The observation that the uptake of two equivalents of base for the formation of the thiolate anion



occurs in one titration step clearly indicates that $pK_r < pK_{R+}$, and the observed $pK_{av} = \frac{1}{2}(pK_r + pK_{R+} + pK_T)$ where $K_T = [73]/[72]$. At $pH = pK_{av}$, equal concentrations of the thiazolium cation 71 and the ring-opened anion 74 are present in equilibrium with only very minor amounts of the pseudobase 72 and neutral thiol (73) (or other tautomeric forms of this

²³⁴ G. D. Maier and D. E. Metzler, *J. Am. Chem. Soc.* **79**, 4386 (1957); E. Yatco-Manzo, F. Roddy, R. G. Yount, and D. E. Metzler, *J. Biol. Chem.* **234**, 733 (1959).

²³⁵ A. Watanabe and Y. Asahi, *J. Pharm. Soc. Jpn.* **75**, 1046 (1955).

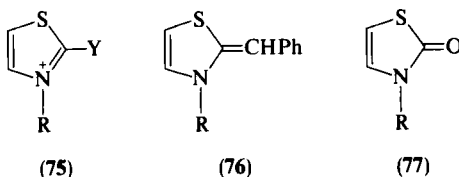
²³⁶ R. R. Williams and A. E. Ruehle, *J. Am. Chem. Soc.* **57**, 1856 (1935).

²³⁷ R. F. W. Hopmann and G. P. Brugnoni, *Nature (London), New Biol.* **246**, 157 (1973).

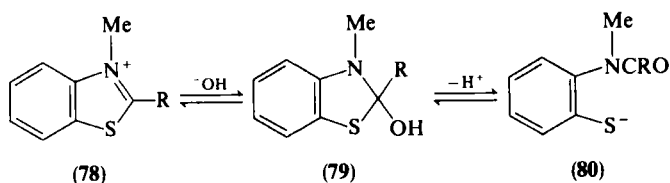
enethiol). Clearly pK_{R^+} for pseudobase formation is considerably higher than pK_a . It is clear that the driving force for these ring-opening reactions is the generation of the conjugate base (thiolate anion **74**) of the relatively acidic thiol **73**.

On the basis of rapid-reaction studies, Hopmann and Brugnoli²³⁷ have claimed $pK_a = 12.7$ for the deprotonation of C-2 of thiamine (**70**) (i.e., ylid formation). This value is much lower than $pK_a \sim 20$ that has been estimated for this deprotonation by Crosby and Lienhard²³⁸ by two different approaches. It seems likely that this $pK_a = 12.7$ is actually pK_{R^+} for pseudobase formation at C-2 in the thiazolium ring of the thiamine cation. Such a pK_{R^+} value is consistent with $pK_{R^+} = 8.3$ for the 3-methylbenzothiazolium cation.⁸³

Clark and Sykes⁶⁶ have investigated the reaction in aqueous base of thiazolium cations **75** bearing a variety of C-2 substituents. Anhydrobases (e.g., **76**) are formed when Y bears an acidic α -hydrogen atom (e.g., Y = $C_6H_5CH_2$, NH_2 , NHR), thiazolin-2-ones (**77**) are produced if Y is a reasonable leaving group (e.g., Y = Br, NR_2), and ring opening occurs in other cases (e.g., Y = H, C_6H_5).



Mills *et al.*²³⁹ first observed that the 3-methylbenzothiazolium cation (**78**; R = H) may be titrated in one step with two equivalents of base to give the ring-opened thiophenol anion (**80**; R = H). This anion is readily air-oxidized in basic solution to the disulfide. The 2,3-dimethylbenzo-



thiazolium cation in aqueous base gives mixtures of the corresponding ring-opened thiophenol anion and the anhydrobase.^{240,241} Analogous

²³⁸ J. Crosby and G. E. Lienhard, *J. Am. Chem. Soc.* **92**, 5707 (1970).

²³⁹ W. H. Mills, L. M. Clark, and J. A. Aeschlimann, *J. Chem. Soc.* **123**, 2353 (1923).

²⁴⁰ L. M. Clark, *J. Chem. Soc.* p. 2313 (1928); p. 2305 (1927).

²⁴¹ W. König and W. Meier, *J. Prakt. Chem. [N.S.]* **109**, 324 (1925).

observations have been made for the corresponding 3-methyl and 2,3-dimethyl benzoselenazolium cations.²⁴⁰ The early studies on benzothiazolium cations have been confirmed more recently.^{67,185,242} Various dimeric species are also obtained when concentrated solutions of benzothiazolium cations are treated with base.^{67,69,186,243-247} The lower pK_{av} values observed for benzothiazolium cations [6.3–6.6 for **78** (R = H)^{156,248,249} and 6.75 for **78** (R = Me)²⁴⁹] than for thiazolium cations are consistent with the expected lower pK_R values for the former than for the latter cations as a result of the stabilizing influence of an annelated benzene ring on pseudobase formation (Section III). This reduction in pK_R clearly more than compensates for the expected increase in pK_T upon going to the benzothiazolium series.

A number of studies have appeared on the pH dependence of the kinetics of the reversible ring opening of thiazolium and benzothiazolium cations. In dilute aqueous base (pH = 9–11), the rate-determining step for ring opening is the addition of hydroxide ion to the thiazolium cation to generate the pseudobase,^{74,154-156} and values of k_{OH} for these cations can be evaluated (see Table VI). The presence of a C-2 methyl substituent slows the rate of ring opening approximately 100-fold due to the steric and electronic hindrance to hydroxide attack.⁷⁴

Vorsanger^{83,249,250} has investigated the kinetics of the interconversion of the *N*-methyl benzothiazolium cations (**78**; R = H, Me) and the corresponding ring-opened thiophenol anions **80** as a function of pH over the range pH = 5–10. In basic solutions, the rate of the ring-opening reaction appears to depend⁸³ upon a rapid equilibration reaction of pK_a 8.30 for R = H and 10.30 for R = Me. Although the pseudobase **79** was not directly observed as a reaction intermediate, it seems likely that these observed pK_a values are actually pK_R values for formation of the pseudobases **79** (R = H) and **79** (R = Me), respectively. However, Vorsanger⁸³ attributes these ionizations to the formation of the ylidic carbanion **81** and anhydrobase **82**, respectively. Detailed stopped-flow kinetic studies and spectral identification of unstable intermediates should allow the further elucidation of the details of these reactions.

²⁴² H. Vorsanger, *Bull. Soc. Chim. Fr.* p. 3118 (1964).

²⁴³ J. Metzger, H. Larivé, R. Dennilauler, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.* p. 2857 (1964).

²⁴⁴ J. Metzger, H. Larivé, R. Dennilauler, R. Baralle, and C. Gaurat, *Bull. Soc. Chim. Fr.* p. 2889 (1964).

²⁴⁵ O. Mumm, H. Hinz, and J. Diedrichsen, *Chem. Ber.* **72**, 2107 (1939).

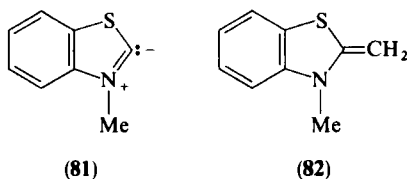
²⁴⁶ H. Larivé and R. Dennilauler, *Chimia* **15**, 115 (1961).

²⁴⁷ A. Wahl and J. J. Vorsanger, *Bull. Soc. Chim. Fr.* p. 3359 (1965).

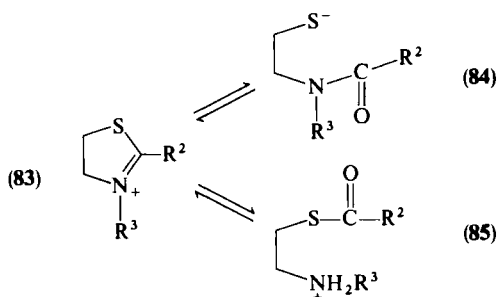
²⁴⁸ R. Breslow, *J. Am. Chem. Soc.* **80**, 3719 (1958).

²⁴⁹ H. Vorsanger, *Bull. Soc. Chim. Fr.* p. 2124 (1967).

²⁵⁰ H. Vorsanger, *Bull. Soc. Chim. Fr.* p. 556 (1967).

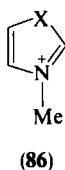


Thiazolinium cations (**83**) undergo similar ring-opening reactions in aqueous solution.^{152,157,251} Whereas the *N*-acyl thiolate anion **84** is the



predominant species present at high pH, the *S*-acyl ammonium cation (**85**) predominates in acidic solutions. Clearly, the pH dependence of the product distribution is determined by the acid-base properties of the thiol and amino groups. Martin and Parcel¹⁵² and Schmir¹⁵⁷ have made detailed kinetic analyses of these equilibrations. Schmir¹⁵⁷ has reported extensive kinetic substituent effects.

Oxazolium¹⁵¹ and benzoxazolium¹⁸⁵ cations undergo ring opening in aqueous solutions even more readily than do their sulfur analogs. Duclos and Haake¹⁵¹ have estimated the relative rates of ring opening of the cations **86** (X = O, S, NMe) to be O:S:NMe = 10^{8.9}:10^{4.6}:1. The pH dependence of the kinetics of ring opening of the 2,3-dimethylbenzoxazolium cation has been investigated.^{163,252}

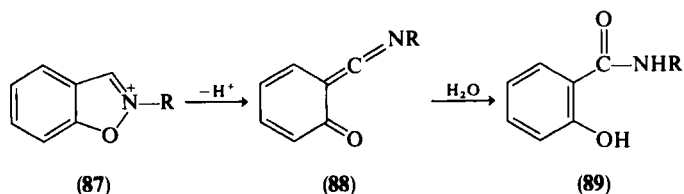


The isoxazolium and benzisoxazolium cations also undergo base-catalyzed ring-opening reactions (e.g., **87** → **89**), however, such reactions appear to

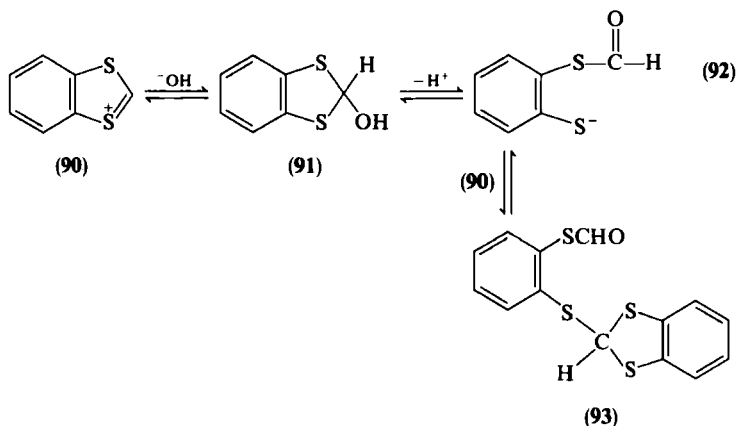
²⁵¹ A. D. Clark and P. Sykes, *J. Chem. Soc. C* p. 103 (1971).

²⁵² L. Oliveros and H. Wahl, *Bull. Soc. Chim. Fr.* p. 2815 (1969).

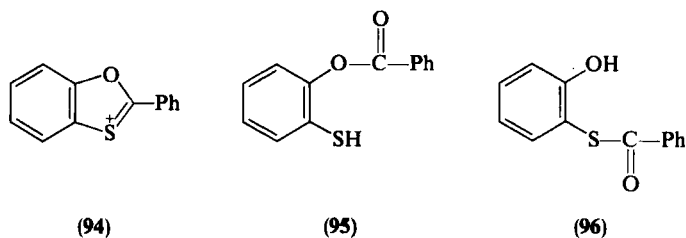
proceed via the ketenimines (e.g., **88**) rather than via pseudobase intermediates.²⁵³⁻²⁵⁵



The 1,3-benzodithiolium and 1,3-benzoxathiolium cations undergo ring-opening reactions readily in aqueous solution. For the parent 1,3-benzodithiolium cation (**90**), the pseudobase intermediate (**91**) has been identified by PMR spectroscopy,⁵⁵ with the ultimate product **93** from this cation being formed by the addition of one ring-opened thiolate anion to another cation.^{55,256} The 2-phenyl-1,3-benzoxathiolium cation



94 ring-opens in aqueous solution to the *O*-benzoyl derivative (**95**) which subsequently rearranges to the corresponding *S*-benzoyl isomer (**96**).¹⁸²



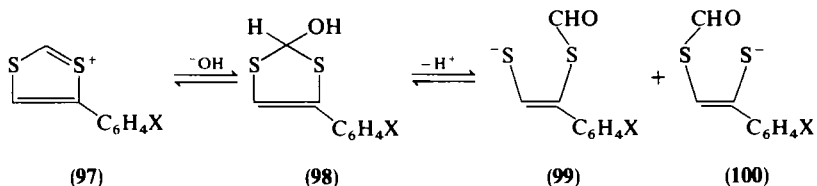
²⁵³ D. S. Kemp and R. B. Woodward, *Tetrahedron* **21**, 3019 (1965).

²⁵⁴ D. S. Kemp, *Tetrahedron* **23**, 2001 (1967).

²⁵⁵ R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.* **83**, 1007 (1961).

²⁵⁶ D. Buza and S. Szymanski, *Rocz. Chem.* **45**, 501 (1971).

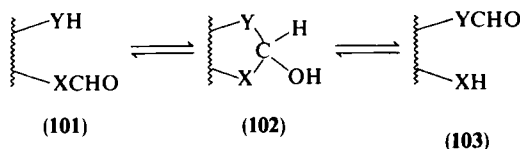
The ring opening of the 4-phenyl-1,3-dithiolium cations (**97**) has been investigated, but the structure of the products (**99** and/or **100**) does not seem to have been established.⁷⁶ The kinetics of the ring opening of a 1,3,4-



thiadiazolium cation²⁵⁷ and various mesoionic species^{258–263} have been reported for a variety of aqueous alcoholic media.

5. Competitive Ring Opening

Two ring-opening reactions are possible when pseudobase formation occurs by hydroxide ion attack at a carbon atom situated between a pair of heteroatoms in a 1,3-relationship (i.e., **102** → **101** or **103**). Several examples



of this phenomenon are adduced (Section V,A,4), and such a situation is formally present for all thiazolium, oxazolium, selenazolium, etc. cations and unsymmetrically substituted imidazolium and 1,3-dithiolium cations and their derivatives. In such cases the direction of ring opening is often determined by the acid–base properties of the XH and YH substituents, and this may often lead to the direction of ring opening being pH-dependent.

The best-studied example of this phenomenon appears to be the situation in aqueous solutions of thiazolinium cations discussed in Section V,A,4. Only C—O bond cleavage is observed for the pseudobase **104** of the *N,O*-trimethylenephthalimidium cation¹⁶⁴ although the products obtained from the tetrahedral intermediate **106** of the iminolactone **105** are

²⁵⁷ P. B. Talukdar and A. Chakraborty, *J. Indian Chem. Soc.* **51**, 600 (1974).

²⁵⁸ S. Aziz, A. F. Cockerill, and J. C. Tillett, *J. Chem. Soc. B* p. 416 (1970).

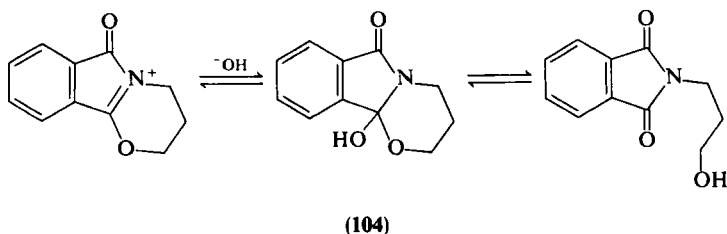
²⁵⁹ E. R. Garrett, *J. Pharm. Sci.* **53**, 42 (1964).

²⁶⁰ E. R. Garrett and P. J. Mehta, *J. Pharm. Sci.* **56**, 1468 (1967).

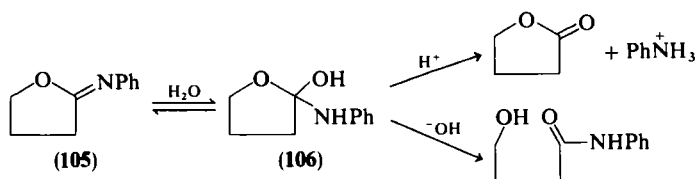
²⁶¹ P. B. Talukdar, S. Banerjee, and A. Chakraborty, *Indian J. Chem.* **10**, 610 (1972).

²⁶² P. B. Talukdar, S. Banerjee, and A. Chakraborty, *Bull. Chem. Soc. Jpn.* **43**, 125 (1970).

²⁶³ S. A. Zotova and V. G. Yashunskii, *J. Org. Chem. USSR (Engl. Transl.)* **3**, 905 (1967).



pH-dependent.^{149,264} In acidic solutions, predominant C—N bond cleavage gives butyrolactone and the anilinium cation, whereas in basic solutions C—O bond cleavage gives 4-hydroxybutyranilide as the major product.



In general, it is essential that product analyses be made for solutions in which thermodynamic control has been established if detailed insight into competitive ring-opening phenomena is to be obtained.

B. PSEUDOBASE ANIONS

For a number of pseudobases, reversible pH-dependent changes in the electronic absorption spectra of their aqueous solutions have been observed at high pH. Such spectral changes are usually much less dramatic than the spectral effects associated with pseudobase formation from the cation and are usually assignable to alkoxide ion formation by deprotonation of the OH group of the pseudobase. Such assignments are supported by the lack of corresponding spectral changes in basic alcoholic solutions and, in a number of cases,^{26,38,89,183} by structural assignment of the alkoxide ions based on their PMR spectra in strongly basic D₂O solutions.

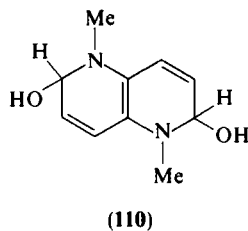
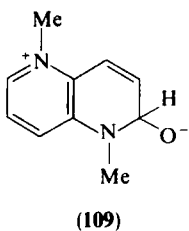
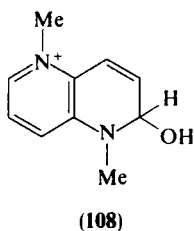
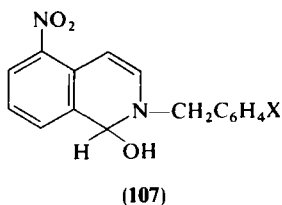
An equilibrium constant $K_{\text{RO-}}$ for alkoxide ion (QO^-) formation may be defined by

$$K_{\text{RO-}} = [\text{H}^+][\text{QO}^-]/[\text{QOH}]$$

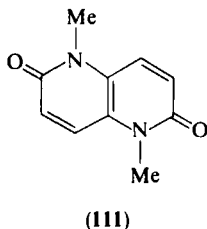
and evaluated from the pH dependence of the absorption spectrum. Literature values currently available for $\text{p}K_{\text{RO-}}$ are in the range 9.7–15 for the

²⁶⁴ B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.* **88**, 551 (1966).

pseudobases of a variety of quinolinium,^{26,87,89,183} isoquinolinium,^{26,265} phthalazinium,²⁶ quinazolinium,²⁶ quinoxalinium,²⁶ and naphthyridinium³⁸ cations. In general, the presence of at least one strongly electron-withdrawing group is necessary to acidify the pseudobase sufficiently to allow the measurement of pK_{RO^-} in aqueous solution. As expected, pK_{RO^-} values for the *N*-benzyl-5-nitroisoquinoline pseudobases (**107**) are almost independent of the substituent X in the benzyl ring.²⁶⁵ The UV and PMR spectral data conclusively indicate³⁸ that the monopseudobases of *N,N'*-dimethyl naphthyridinium dications form alkoxide ions in basic solutions (e.g., **109** from **108**) rather than adding a second hydroxide ion to form dipseudobase species (e.g., **110**). This is consistent with the expected high pK_R for pseudo-



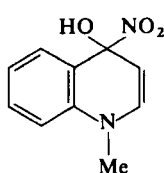
base formation in the pyridinium ring of **108**. However, the presence of minor amounts of **110** is suggested by the isolation of the 1,5-naphthyridine-dione **111** upon ferricyanide oxidation of basic aqueous solutions.³⁸ Similar observations have been made for dications of 1,6- and 2,7-naphthyridines.³⁸



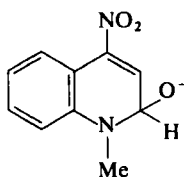
Spectral and kinetic data⁸⁹ are consistent with the C-4 adduct **112** being the predominant pseudobase present in neutral or weakly basic solutions

²⁶⁵ J. W. Bunting, P. A. Lee-Young, and D. J. Norris, *J. Org. Chem.* **43**, 1132 (1978).

of the 1-methyl-4-nitroquinolinium cation; but the alkoxide ion **113** derived from the C-2 pseudobase is the predominant species in more basic solutions.



(112)



(113)

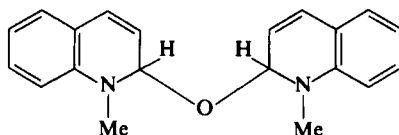
Thus, the alkoxide ion derived from **112** is the kinetically preferred species, whereas the C-2 alkoxide ion **113** is the thermodynamically more stable species. In this case, the measured equilibrium pK_{RO^-} value is actually an apparent ionization constant defined by

$$K_{RO^-}^{app} = \frac{[H^+]([Q^2O^-] + [Q^4O^-])}{[Q^2OH] + [Q^4OH]} \approx \frac{[H^+][Q^2O^-]}{[Q^4OH]}$$

for predominance by **112** (Q^4OH) and **113** (Q^2O^-) in neutral and basic solutions, respectively.

C. BIMOLECULAR ETHERS

In 1899, Hantzsch and Kalb³ claimed the isolation of the "bimolecular ether" **114** from basic aqueous solutions of the 1-methylquinolinium cation. This reaction appears in most textbooks of heterocyclic chemistry and is



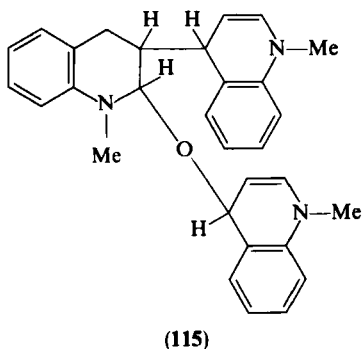
(114)

readily rationalized in terms of the nucleophilic attack of the pseudobase alkoxide ion on a second 1-methylquinolinium cation. However, recent spectral investigations^{70,266,267} have shown that Hantzsch's compound displays three distinct *N*-methyl peaks in its PMR spectrum and so clearly cannot be the bimolecular ether **114**. Mass spectral investigation²⁶⁷ indicates a molecular formula $C_{30}H_{31}N_3O$ which indicates the presence of three *N*-methylquinoline moieties and so is consistent with the PMR spectral

²⁶⁶ H. Vorsanger and J. J. Vorsanger, *Bull. Soc. Chim. Fr.* p. 589 (1970).

²⁶⁷ H. Vorsanger and J. J. Vorsanger, *Bull. Soc. Chim. Fr.* p. 593 (1970).

result. On the basis of detailed structural studies via mass spectrometry and PMR spectroscopy making use of quinolines bearing specific deuterium labels, Vorsanger and Vorsanger^{266,267} have suggested the structure **115**



and have proposed a mechanism for formation of this molecule. Hantzsch's product actually contains a small amount of 1-methyl-2-quinolinone, and the elemental analysis of this product in which **115** is contaminated with the quinolinone is identical to the elemental composition of **114**.

There are a number of claims^{4,40,51,69,150,247,268-274} for the isolation of bimolecular ethers from various other heterocyclic cations although the structures of these products have rarely been unambiguously established. The reaction mechanism outlined for the formation of **114** probably does occur in other heterocyclic systems, particularly in those cases in which alkoxide ion formation from the pseudobase readily occurs. Solubility considerations may dictate the precipitation of the bimolecular ether rather than the pseudobase from basic aqueous solutions containing relatively high concentrations of the heterocycle. However, such bimolecular ether formation will usually be in direct competition with the pseudobase disproportionation reaction (Section V,D) which shows the same pH dependence.

Ether formation would be expected to be more efficient when it can occur intramolecularly rather than intermolecularly. Several examples (**116**–**118**) of the isolation of "intramolecular ethers" of this type have been reported.^{227,275,276}

²⁶⁸ A. Alemagna and T. Bacchetti, *Gazz. Chim. Ital.* **102**, 1077 (1972).

²⁶⁹ I. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 151 (1965).

²⁷⁰ M. D. Johnson, *J. Chem. Soc.* p. 283 (1962).

²⁷¹ S. V. Krivun and S. V. Dul'skaya, *Khim. Geterotsikl. Soedin.* p. 1454 (1970).

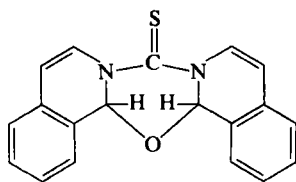
²⁷² K. Lempert and P. Gyulai, *Z. Chem.* **10**, 384 (1970).

²⁷³ K. Lempert and P. Gyulai, *Tetrahedron* **26**, 3443 (1970).

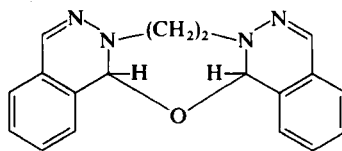
²⁷⁴ H. Minato, E. Yamazaki, and M. Kobayashi, *Chem. Lett.* p. 525 (1976).

²⁷⁵ H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **40**, 918 (1957).

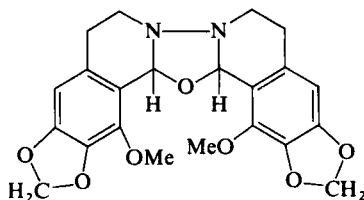
²⁷⁶ D. Korbonits and S. Harsanyi, *Chem. Ber.* **99**, 273 (1966).



(116)



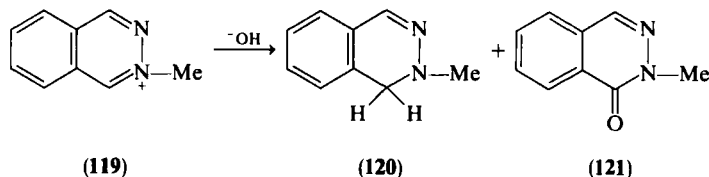
(117)



(118)

D. DISPROPORTIONATION

The disproportionation of heteroaromatic cations in aqueous base has been known for many years.²⁷⁷⁻²⁷⁹ For example, fresh organic extracts of basic aqueous solutions of the 2-methylphthalazinium cation (119) contain^{26,277,280} a mixture of 2-methyl-1,2-dihydrophthalazine (120) and 2-methyl-1-phthalazinone (121). Similar reactions have been reported for



pyridinium,²¹⁷ isoquinolinium,^{281,282} benzothioapyrylium,⁴⁰ quinazolinium,²⁷² acridinium (122; X = NR),²⁷⁹ xanthylum (122; X = O),²⁸³ thioxanthylum (122; X = S),^{283,284} and phenanthridinium²⁷⁹ cations.

²⁷⁷ S. Gabriel and F. Muller, *Chem. Ber.* **28**, 1830 (1895).

²⁷⁸ J. Gadamer, *Arch. Pharm. (Weinheim, Ger.)* **243**, 31 (1905).

²⁷⁹ A. Pictet and E. Patry, *Chem. Ber.* **35**, 2534 (1902).

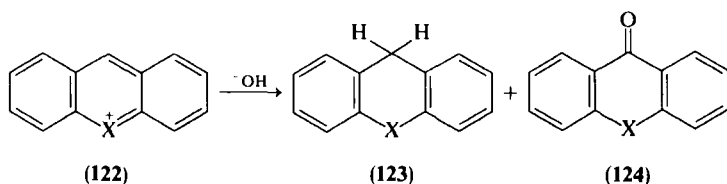
²⁸⁰ R. F. Smith and E. D. Otremba, *J. Org. Chem.* **27**, 879 (1962).

²⁸¹ D. W. Brown and S. F. Dyke, *Tetrahedron* **22**, 2429 (1966).

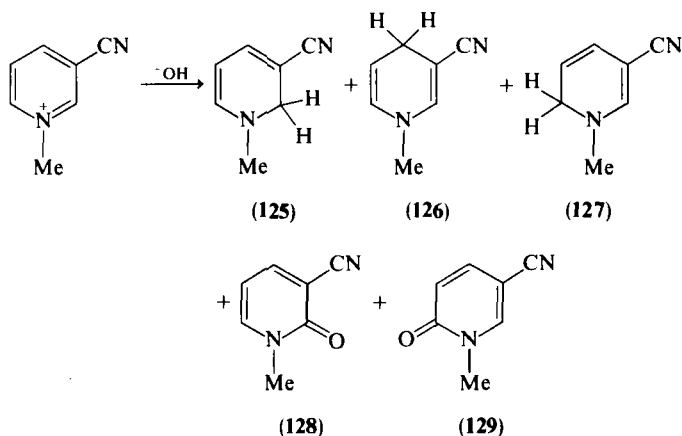
²⁸² D. W. Brown, M. Sainsbury, S. F. Dyke, and W. G. D. Lugton, *Tetrahedron* **27**, 4519 (1971).

²⁸³ J. Ashby, M. Ayad, and O. Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1* p. 1104 (1973).

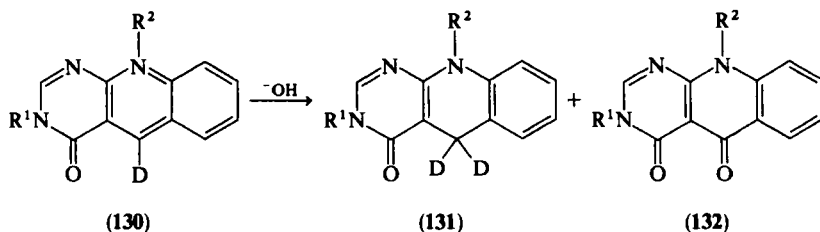
²⁸⁴ C. V. T. Campbell, A. Dick, J. Ferguson, and J. D. London, *J. Chem. Soc.* p. 747 (1941).



In all cases, the cations display spectral changes consistent with pseudobase formation at electronic spectral concentrations, with the disproportionation reaction becoming important at much higher concentrations of the heterocycle. This concentration dependence indicates the bimolecular nature of these reactions, and the 1:1 ratio of oxidized and reduced products, in those cases which have been carefully investigated, is indicative of a true disproportionation reaction. A particularly interesting case is the report²¹⁷ of equimolar amounts of dihydropyridines (a mixture of **125** – **127**) and pyridinones (a mixture of **128** and **129**) from the reaction of the 1-methyl-3-cyanopyridinium cation in aqueous base. The 1:1 ratio of oxidized and reduced products is sometimes obscured by subsequent air oxidation of the reduced product to the oxidized product.



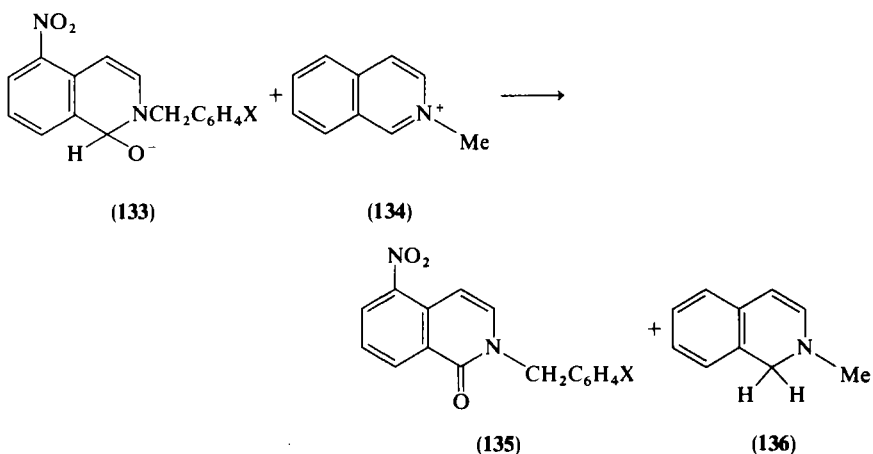
The bimolecular nature of the reaction has also been established^{110,111} by deuterium labeling experiments in the case of the pyrimido[4,5-*b*]-quinolinium cations **130**. Reduced product **131** is doubly labeled with deuterium; no deuterium is incorporated into the reduced product when the unlabeled cation is allowed to disproportionate in D_2O . Clearly, hydrogen transfer during disproportionation occurs without exchange with solvent protons; thus, direct interaction between two heterocyclic molecules is indicated.



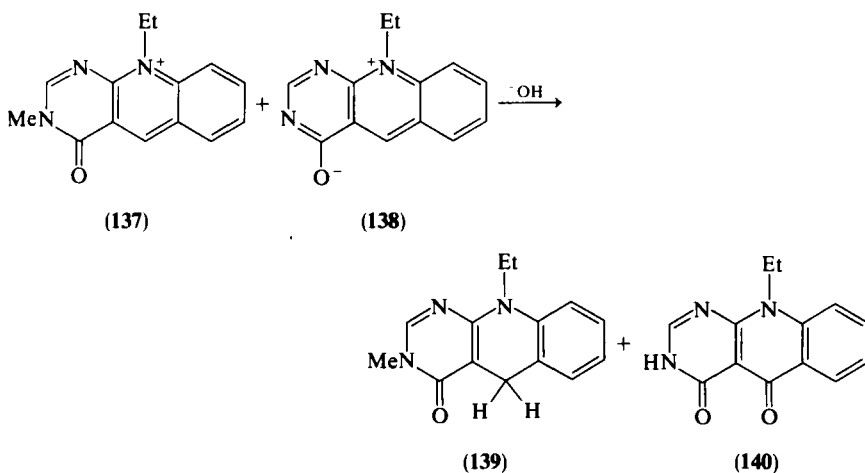
Disproportionation for the 2-methylphthalazinium cation occurs only in the pH range 10–13, with the pseudobase itself being extracted from more basic aqueous solutions in which the pseudobase alkoxide ion ($pK_{RO^-} = 13.0$) predominates.²⁶ Although no detailed kinetic study of the pH dependence of these disproportionation reactions has appeared, these qualitative observations suggest that the rate of disproportionation reaches a maximum value at the pH at which the concentration of the pseudobase is at its maximum value. At first glance, this result seems to suggest that the alkoxide ion is stable toward disproportionation and that this reaction proceeds via the pseudobase itself in aqueous solution but not in organic solvent. However, this interpretation is not consistent with the observed stability of many pseudobases to disproportionation, and it is difficult to conceive of a mechanism for a disproportionation via two molecules of the pseudobase. A kinetically equivalent mechanism for the reaction of two molecules of the pseudobase is the reaction of the pseudobase alkoxide ion with the heterocyclic cation as has been suggested¹⁴ for the disproportionation of the pseudobase of berberine to oxyberberine and dihydroberberine. In this case disproportionation would be expected to occur most readily in those heterocyclic systems in which reasonable concentrations of cation and pseudobase anion can be obtained simultaneously. This implies disproportionation for those cations which have pK_{R^+} and pK_{RO^-} of similar magnitude, particularly in those cases where $pK_{R^+} \geq pK_{RO^-}$. An example of the latter situation is the 1-methylquinolinium cation which irreversibly forms 1-methyl-2-quinolinone in very basic aqueous solutions without undergoing any spectral changes consistent with reversible pseudobase formation.²⁶

This interpretation of the mechanism of disproportionation is supported by two observations on "crossed disproportionation" reactions. In a kinetic study²⁸⁵ of the reduction of the 2-methylisoquinolinium cation by a series of 2-benzyl-5-nitroisoquinolinium cations, the pH dependence of the reaction was observed to be consistent with hydride transfer from the pseudobase alkoxide ion **133** to the 2-methylisoquinolinium cation. Clark and Parvizi¹¹¹

²⁸⁵ J. W. Bunting and S. H. Kabir, *J. Org. Chem.* **43**, 3662 (1978).

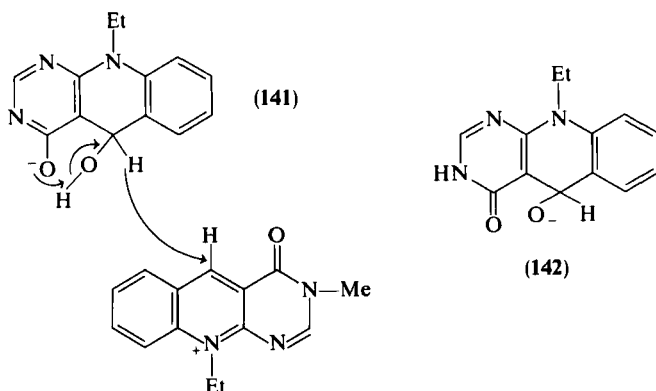


have observed that **137** and **138** react to give the products **139** and **140** at pH 10.2 much faster than the self-disproportionation of each individual cation at this pH. These workers interpret the mechanism of hydride transfer



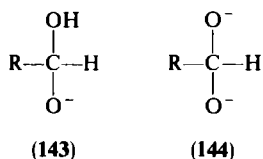
in this reaction as being via transition state **141**; however, the alkoxide ion **142** could act as hydride donor in a kinetically equivalent mechanism to **141**. It should also be noted, that the ease with which disproportionation occurs in the xanthylum and thioxanthylum series^{283,284,286} which have very low pK_R^+ values (Table I) suggests that neutral pseudobases may act as hydride donors towards very reactive cationic hydride acceptors. Related

²⁸⁶ E. D. Amstutz and C. R. Neumoyer, *J. Am. Chem. Soc.* **69**, 1925 (1947).



intermolecular hydride transfers to pyrylium and benzopyrylium cations have also been observed for other nucleophilic addition reactions.^{287,288}

Habermehl and Schunk²⁸⁹ have drawn attention to the analogy between the pseudobase disproportionation and the Cannizzarro reaction of aldehydes, which can be considered to be a disproportionation of the aldehyde hydrate to a carboxylic acid and alcohol. This reaction is usually considered to involve hydride transfer from either the mono- or dianion (i.e., **143** or **144**) of the aldehyde hydrate to the carbonyl group of another aldehyde molecule. The anions **143** and **144** are clearly quite similar electronically



to the pseudobase anion which is suggested above to be involved in hydride transfer to a heterocyclic cation in pseudobase disproportionation.

E. OTHER REACTIONS VIA PSEUDOBASE INTERMEDIATES

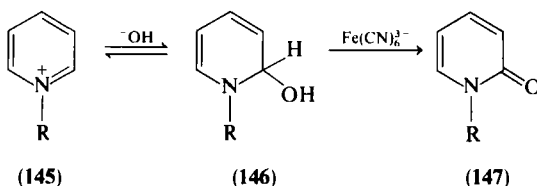
There are many examples in the literature of reactions of heterocyclic molecules which have been postulated to proceed via pseudobase intermediates. While most of these reaction mechanisms seem to be chemically reasonable, in most cases the participation of the pseudobase in the reaction has not been definitely established by kinetics, spectral studies, substituent

²⁸⁷ E. T. Ostensen, *Acta Chem. Scand. Ser. B* **28**, 1107 (1974).

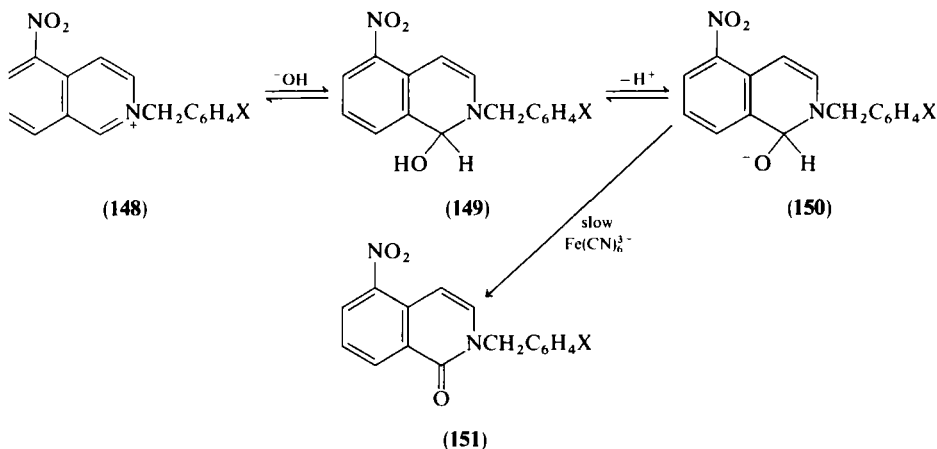
²⁸⁸ E. T. Ostensen, *Acta Chem. Scand. Ser. B* **29**, 787 (1975).

²⁸⁹ G. Habermehl and J. Schunck, *Justus Liebigs Ann. Chem.* **750**, 128 (1971).

effects, etc. A typical example of this situation is the oxidation of heteroaromatic cations by ferricyanide ion in aqueous base, which was first investigated in detail by Decker²⁹⁰⁻²⁹² for the oxidation of pyridinium cations (**145**) to 2-pyridinones (**147**). Although this reaction is usually proposed to



proceed via ferricyanide attack on the pseudobase (e.g., **146**), it is only recently^{265,293} that any attempt has been made to corroborate this assumption with a study of the pH dependence of the rate of oxidation. For the oxidation of 2-benzyl-5-nitroisoquinolinium cations (**148**) to the corresponding isoquinolinones (**151**), the reaction has been shown to be first-order in both heterocycle and ferricyanide and to display a pH dependence that is consistent with rate-determining ferricyanide ion attack on the pseudobase anion (**150**).²⁶⁵ Substituent effects (X in **148**) and kinetic isotope effects for the 1-deuterio compound are consistent with rate-determining abstraction of hydride ion from **150** by ferricyanide.²⁶⁵



The bromination of various nitrogen heterocycles has been shown to proceed via pseudobase or covalent hydrate intermediates. Tee *et al.*^{57,100,294}

²⁹⁰ H. Decker, *Chem. Ber.* **25**, 443 (1892).

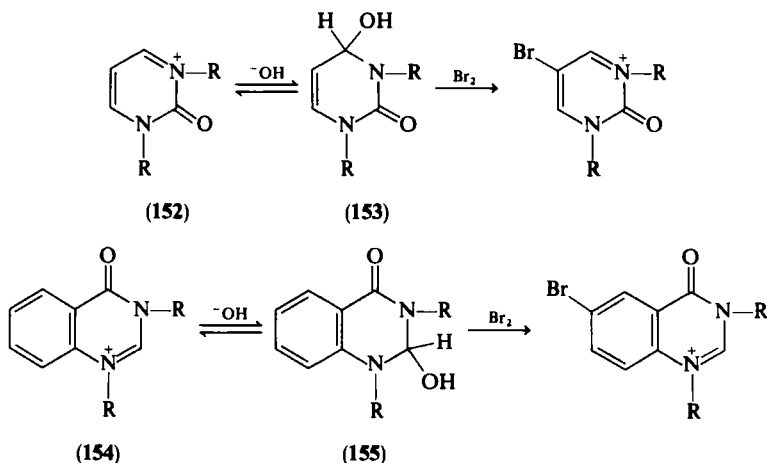
²⁹¹ H. Decker, *J. Prakt. Chem.* [N.S.] **47**, 28 (1893).

²⁹² H. Decker and A. Kaufmann, *J. Prakt. Chem.* [N.S.] **84**, 425 (1911).

²⁹³ E. Tomilenko, *Zh. Vses. Khim. O-va.* **21**, 462 (1976); *Chem. Abstr.* **85**, 159094 (1976).

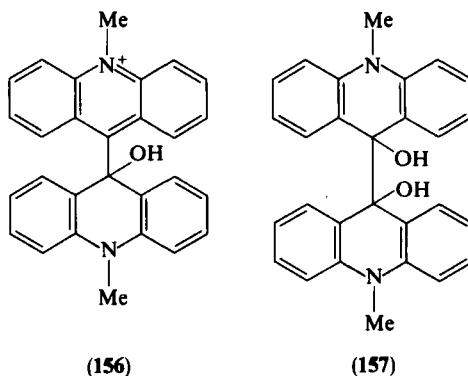
²⁹⁴ O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.* p. 1032 (1972).

have established that the pH dependence of the bromination of 2-oxo-pyrimidinium (152) and 4-oxoquinazolinium (154) cations in aqueous solution is consistent with bromine attack on the pseudobases 153 and 155, respectively. Similar less detailed observations have also been reported



for the bromination of quinolinium²⁹⁵ and isoquinolinium²⁹⁶ cations.

Pseudobases have often been postulated as intermediates in the chemiluminescent oxidation of acridinium cations to acridinones.^{103,297-299} Both the mono- and dipseudobases (156 and 157) of lucigenin have been proposed as intermediates in the chemiluminescent oxidation of this cation in basic solutions.



²⁹⁵ M. D. Johnson and J. H. Ridd, *J. Chem. Soc.* p. 291 (1962).

²⁹⁶ M. D. Johnson, *J. Chem. Soc.* p. 200 (1964).

²⁹⁷ K. Gleu and W. Petsch, *Z. Angew. Chem.* **48**, 57 (1935).

²⁹⁸ F. McCapra, *Q. Rev. Chem. Soc.* **20**, 485 (1966).

²⁹⁹ E. G. Janzen, J. P. Pickett, J. W. Happ, and W. DeAngelis, *J. Org. Chem.* **35**, 88 (1970).

Various decomposition reactions of heterocyclic cations in aqueous solution are expected to proceed via pseudobase intermediates. These intermediates have been established for the alkaline decomposition of the pyridinium ring of nicotinamide adenine dinucleotide³⁰⁰ and for various solution transformations of flavin-derived cations.^{112,113,301-303} Nucleophilic substitution by hydroxide ion in various heteroaromatic cations almost certainly proceeds via the appropriate pseudobase σ -complexes.^{304,305}

These examples, in conjunction with those in Sections V,A, C, and D, are merely representative of a large body of heterocyclic chemistry based on pseudobase species. In general, detailed kinetic and mechanistic studies of these reactions are few at the present time, and future quantitative studies in this area should provide many mechanistic insights and satisfying rewards to the physical-organic chemist.

VI. Pseudobase Formation in Nonaqueous Solvents

A. ALCOHOLS AND AQUEOUS ALCOHOLIC MEDIA

As indicated earlier (Section II), pseudobase formation by addition of alkoxide ion to an unsaturated heterocyclic cation in basic alcoholic solution is exactly analogous to hydroxide ion addition in aqueous base. There are numerous reports in the literature of pseudobases, which had been isolated from aqueous solution, being converted into the corresponding alkoxide adducts upon recrystallization from alcoholic solvents. Although the term "pseudobase" was originally defined^{2,3} for hydroxide adducts in aqueous solution, there has been a tendency in the recent literature to use this term also for alkoxide adducts in alcoholic solutions. Such usage requires that the term "pseudobase" be understood to refer to a class of reaction product rather than to a particular chemical species (i.e., the hydroxide adduct) in aqueous media. It also follows that "pseudobase" is meaningless when used in this way unless a particular solvent is also indicated. It seems reasonable to generalize "pseudobase formation" in this way for a variety of solvents; however, an uncertainty is introduced when "pseudobase formation" is referred to in aqueous alcoholic media, since the "pseudobases" in such media will be mixtures of the hydroxide and alkoxide adducts.

³⁰⁰ C. C. Guilbert and S. L. Johnson, *Biochemistry* **16**, 335 (1977).

³⁰¹ K. H. Dudley and P. Hemmerich, *J. Org. Chem.* **32**, 3049 (1967).

³⁰² S. B. Smith and T. C. Bruice, *J. Am. Chem. Soc.* **97**, 2875 (1975).

³⁰³ H. I. X. Mager, *Tetrahedron* **33**, 981 (1977).

³⁰⁴ G. B. Barlin and J. A. Benbow, *J. Chem. Soc., Perkin Trans. 2* p. 790 (1974).

³⁰⁵ G. B. Barlin and J. A. Benbow, *J. Chem. Soc., Perkin Trans. 2* p. 298 (1975).

TABLE VII
RATE AND EQUILIBRIUM CONSTANTS FOR ADDITION OF HYDROXIDE AND
ALKOXIDE IONS TO **158**^a

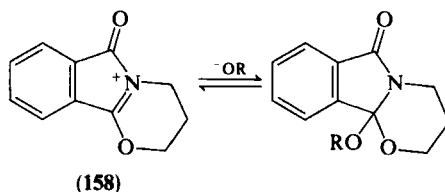
ROH	k_{OR} ($M^{-1} \text{ sec}^{-1}$)	k_{ROH} ($M^{-1} \text{ sec}^{-1}$)	k_2 (sec^{-1})	k_1 ($M^{-1} \text{ sec}^{-1}$)	K (M^{-1})
H ₂ O	4.6×10^6	1.0^b			3×10^{20c}
MeOH	4×10^7	5.3	4.4×10^{-8}	19.9	1.5×10^{15}
EtOH	5×10^7	3.7	3.3×10^{-8}	24.6	9×10^{14}
CHCl ₂ CH ₂ OH	1.7×10^7	1.0	8.5×10^{-6}	3.7	2×10^{12}
CF ₃ CH ₂ OH	3.3×10^7	0.62	8.4×10^{-5}	4.2	4×10^{11}

^a Data from Gravitz and Jencks,³⁰⁶ at 25°.

^b Corrected for $[\text{H}_2\text{O}] = 55 M$.

^c Calculated from data in Gravitz and Jencks.¹⁶⁴

While quantitative measurements of pseudobase formation in aqueous alcoholic solutions may be used as indications of the relative susceptibilities to nucleophilic attack for closely related cations,^{9,53,75,218} such data are not directly comparable with equilibrium and rate data for pseudobase formation in either water or the pure alcohol (or even with data in aqueous alcoholic solutions of other compositions). Several workers^{218,257,261,262} have reported rate constants for "hydroxide ion" attack on heterocyclic cations in aqueous alcoholic solutions without any apparent attempt to consider the complications that arise in such media as a result of the competition between hydroxide and alkoxide ions as nucleophiles. The only attempt to measure the relative reactivities of hydroxide and alkoxide ions toward a heterocyclic cation appears to be the work of Gravitz and Jencks³⁰⁶ for the *N,O*-trimethylenephthalimidium cation (**158**). In this study, product analysis indicated the relative proportions of hydroxide and alkoxide adduct

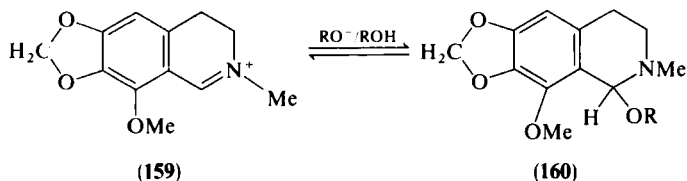


for dilute solutions of a number of alcohols in water. Rate and equilibrium data from this study are summarized in Table VII.

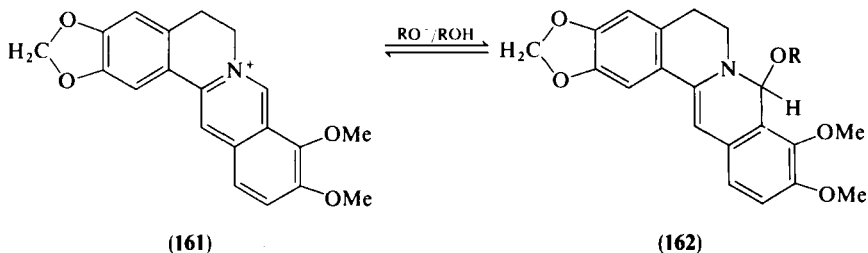
There have been relatively few quantitative studies of cation–pseudobase equilibration in alcohols. Values of pK_R in methanol are: 16.9 for **75** ($R = \text{Me}$; $Y = \text{Ph}$),⁹⁰ 7.3 for **78** ($R = \text{Me}$),⁹⁰ 8.2 for **83** ($R^2 = \text{Ph}$; $R^3 = \text{Me}$),⁹⁰ 13.5–17.0 for various **163**,⁵¹ and 13.8–16.5 for various alkaloidal isoquinolinium cations related to berberine.¹⁰ In general, one would predict

³⁰⁶ N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 507 (1974).

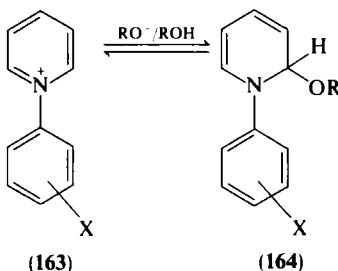
increased stability for pseudobases relative to their cations in alcohols than in water due to (1) the increased difficulty in solvating the cation in solvents of lower dielectric constant than water and (2) the enhanced nucleophilicity of alkoxide ions in alcohol solution relative to the hydroxide ion in water. The few data that are presently available seem to support this hypothesis. Thus, Skinner¹³⁴ reported $K = 36 M^{-1}$ in water and $K = 4.7 \times 10^3 M^{-1}$ in ethanol for pseudobase formation (**160**; R = H, Et, respectively) by the cotarnine cation (**159**). Simanek *et al.*¹⁰ report $K = 20 M^{-1}$ for pseudobase



(**162**; R = Me) formation by the berberine cation (**161**) in methanol, while Skinner¹³⁴ gives $K = 3.8 \times 10^3 M^{-1}$ for this same cation in ethanol. Kaválek *et al.*⁵² found $K(\text{EtOH})/K(\text{MeOH}) \approx 300$ for C-2 adduct (**164**)



formation by three *N*-(substituted phenyl) pyridinium cations (**163**). For **163**, K for methoxide addition in methanol is correlated with Hammett σ°



values for X by Eq. (38) ($r = 0.995$).³⁰⁷

$$\log K = 3.56 \sigma^\circ + 0.30 \quad (38)$$

³⁰⁷ Kaválek *et al.*⁵² give $\log K = 3.27 \sigma^\circ + 0.07$ for this correlation, with the data for X = 4-NO₂ not fitting the correlation line. In fact this equation does not reproduce the data of Kaválek *et al.*⁵² Equation (38) was calculated for the present review using Wells' table³⁰⁸ of Hammett σ° values and includes the 4-NO₂ substituent.

It is unfortunate that there has been so little work devoted to quantitative measurements of cation–pseudobase equilibria in methanol and ethanol since these media have several advantages over water for the determination of the relative susceptibilities of heterocyclic cations to pseudobase formation. The enhanced stability of the pseudobase relative to the cation in alcohols compared to water is discussed earlier; this phenomenon will permit the quantitative measurement of pseudobase formation in methanol (and especially ethanol) for many heterocyclic cations for which the equilibrium lies too far in favor of the cation in aqueous solution to allow a direct measurement of the equilibrium constant. Furthermore, the deprotonation of hydroxide pseudobases (Section V,B) and the occurrence of subsequent irreversible reactions (Sections V,C and D), which complicate measurements for $pK_{R^+} > 14$ in aqueous solutions, are not problems in alcohol solutions. Data are now available for the preparation of buffer solutions in methanol over a wide range of acidities.^{309–312} An appropriate basicity function scale will be required for more basic solutions. The series of *N*-(substituted phenyl)pyridinium cations (163) studied by Kavalek *et al.*⁵² should be suitable for use as indicators in at least some of the basic region. The H_m and J_m basicity functions³¹³ should not be assumed⁹⁰ to apply to methoxide ion addition to heterocyclic cations because of the differently charged species involved in the indicators used to construct these scales.

Beranek *et al.*³¹⁴ report a 600-fold enhancement in equilibrium constant for methoxide addition to pyridinium cations in 1:1 dimethyl sulfoxide–methanol relative to methanol. These workers have also measured the rates of dissociation of the methoxide adducts of *N*-phenylpyridinium cations (163) in dimethyl sulfoxide–methanol mixtures and have used the observation that the relative rates of dissociation appear to be independent of dimethyl sulfoxide content of the solvent to extrapolate these data to pure methanol. The rates of dissociation for all substituents other than $X = 3\text{-NO}_2$ or 4-NO_2 are too rapid in 100% methanol to allow direct determination by stopped-flow spectrophotometry. The presence of dimethyl sulfoxide shifts the equilibrium toward the adduct both by enhancing the rate of methoxide addition and by decreasing the rate of adduct dissociation. These solvent effects on pseudobase formation are similar to those observed

³⁰⁸ P. R. Wells, "Linear Free Energy Relationships," p. 15. Academic Press, New York, 1968.

³⁰⁹ C. L. de Ligny, P. F. M. Luky, M. Rehbach, and A. A. Wieneke, *Recl. Trav. Chim. Pays-Bas* **79**, 713 (1960).

³¹⁰ C. H. Rochester, *J. Chem. Soc. B* p. 33 (1967).

³¹¹ C. H. Rochester and B. Rossall, *Trans. Faraday Soc.* **65**, 1004 (1969).

³¹² M. J. Cook, A. R. Katritzky, and A. D. Page, *Tetrahedron* **31**, 2707 (1975).

³¹³ C. H. Rochester, "Acidity Functions," pp. 246 and 250. Academic Press, New York, 1970.

³¹⁴ V. Beránek, A. Lyčka, and V. Štěrbá, *Collect. Czech. Chem. Commun.* **40**, 1919 (1975).

for Meisenheimer complex formation.³¹⁵⁻³¹⁷ For ethanol solutions, the association rate is larger and the dissociation rate is smaller than in methanol.⁵²

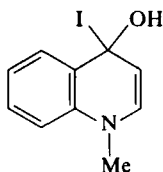
The k_2 values in 1:1 dimethyl sulfoxide-methanol are correlated by Eq. (39) ($r = 0.9985$), which indicates a similar ρ value to $\rho = -1.52$ for the rates of dissociation of cyanide ion from 1-(substituted phenyl)-4-cyano-

$$\log k_2 = -1.90 \sigma^\circ + 2.51 \quad (39)$$

1,4-dihydropyridines in methanol.⁴⁹ Comparison of the ρ values of Eqs. (38) and (39) indicates that the transition state for the formation (and dissociation) of these adducts is approximately midway between cation and pseudobase.

B. HETEROCYCLIC MEISENHEIMER COMPLEXES

Pseudobase formation by nucleophilic addition to heteroaromatic cations is closely related to the long-known Meisenheimer complex formation by nucleophilic addition to an electron-deficient neutral aromatic molecule.²⁰⁻²⁵ In both cases nucleophilic attack on an electron-deficient aromatic ring produces a σ -complex—an anionic Meisenheimer complex or a neutral pseudobase molecule. Despite the intense interest over the past few years in Meisenheimer complexes as models for σ -complex intermediates in nucleophilic aromatic substitution reactions, there has been little overt recognition of the relationship between Meisenheimer complexes and pseudobases derived from heteroaromatic cations. In this regard, it is interesting that the pseudobase **165**, which can be regarded as the σ -complex intermediate that would be expected for an S_NAr reaction between the 1-methyl-4-iodoquinolinium cation and hydroxide ion, has been spectroscopically characterized.⁸⁹



(165)

Apart from the electrical charges of the species involved, there is no fundamental reason for distinguishing between pseudobase formation and

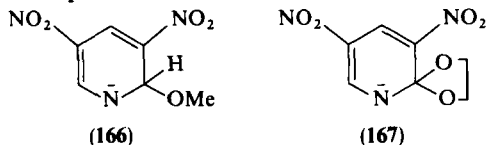
³¹⁵ A. J. Parker, *Chem. Rev.* **69**, 1 (1969).

³¹⁶ J. W. Larsen, K. Amin, and J. H. Fendler, *J. Am. Chem. Soc.* **93**, 2910 (1971).

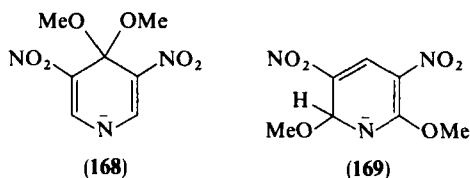
³¹⁷ J. H. Fendler and J. W. Larsen, *J. Org. Chem.* **37**, 2608 (1972).

Meisenheimer complex formation as separate reactions. Meisenheimer complexes can be considered as the anionic pseudobases derived from neutral aromatic molecules, and in this light it is clear that heterocyclic Meisenheimer complexes are appropriately considered in the current Review. By so doing, it is hoped that attention can be drawn to potentially mutual benefits that may be derived from comparative studies of neutral and anionic pseudobases. Certainly, the spectroscopic techniques applicable to the study of pseudobase and Meisenheimer complex formation are identical. Quantitative studies of substituent effects and structural effects on rates and equilibria for nucleophilic addition should be relevant both to neutral and to anionic σ -complex formation. The general rules enunciated by Strauss^{23,318} and Fendler³¹⁹ for the prediction of the relative stabilities of Meisenheimer complexes should be directly applicable to analogous pseudobases. Terrier *et al.*²⁷ have made an important contribution in this area with a detailed comparison of kinetic and thermodynamic parameters for formation of a benzofuroxan Meisenheimer complex and an isoquinoline pseudobase.

The first examples of heterocyclic Meisenheimer complexes were reported in 1968 for 3,5-dinitropyridines. Fyfe presented³²⁰ UV and PMR spectral evidence for C-2 addition of methoxide ion to 3,5-dinitropyridine to give **166**. Similar spectroscopic evidence for



Meisenheimer complex formation from the 2-dimethylamino and 2-(2-hydroxyethyl) derivatives was also obtained. In the latter case, the intramolecular σ -complex **167** is suggested.³²⁰ Dickeson *et al.*³²¹ and Illuminati *et al.*^{322,323} reported the isolation of the sodium salt of the C-4 methoxide adduct (**168**) of 3,5-dinitro-4-methoxypyridine, and rate and equilibrium



³¹⁸ R. M. Murphy, C. A. Wulff, and M. J. Strauss, *J. Am. Chem. Soc.* **96**, 2678 (1974).

³¹⁹ J. H. Fendler, W. L. Hinze, and L.-J. Liu, *J. Chem. Soc., Perkin Trans. 2* p. 1768 (1975).

³²⁰ C. A. Fyfe, *Tetrahedron Lett.* p. 659 (1968).

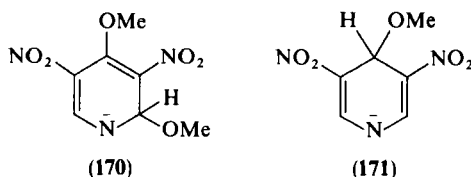
³²¹ J. E. Dickeson, L. K. Dyall, and V. A. Pickles, *Aust. J. Chem.* **21**, 1267 (1968).

³²² G. Illuminati and F. Stegel, *Tetrahedron Lett.* p. 4169 (1968).

³²³ P. Bemporad, G. Illuminati, and F. Stegel, *J. Am. Chem. Soc.* **91**, 6742 (1969).

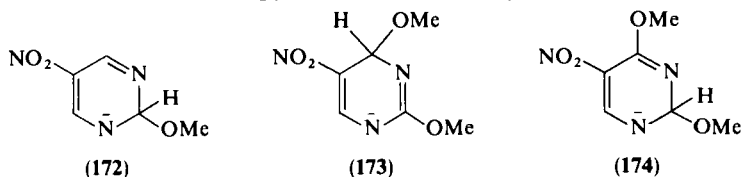
constants for the formation of **168** in methanol have been measured.³²³ 3,5-Dinitro-2-methoxypyridine forms the C-6 methoxide adduct (**169**), the structure of which was established by PMR spectroscopy using appropriate deuterium-labeled species.^{322,324} Equilibrium constants for the formation of **168** and **169** (Table IX) indicate the former to be considerably more stable relative to its aromatic precursor than the latter.

Subsequent work has shown that care should be taken in the use of dimethyl sulfoxide as a solvent for PMR spectral studies of Meisenheimer complexes. Biffin *et al.*³²⁵ found that the kinetically controlled methoxide adduct of 3,5-dinitro-4-methoxypyridine in dimethyl sulfoxide solutions was the C-2 adduct **170** which took 72 hours at 27° to rearrange completely



to the thermodynamically more stable **168**. The rate of this equilibration was considerably increased by the addition of methanol. Terrier *et al.*³²⁶ made a detailed kinetic study of this phenomenon at several temperatures in methanol–dimethyl sulfoxide mixtures of various compositions. It was also observed^{327,328} that **171** is the kinetically controlled methoxide adduct of 3,5-dinitropyridine for solutions rich in dimethyl sulfoxide rather than the thermodynamically more stable **166**. Detailed studies of the influence of dimethyl sulfoxide on the kinetics and equilibrium of the equilibration of 3,5-dinitropyridine with its methoxide and hydroxide adducts have also been reported.³²⁸

PMR and UV spectral evidence have been reported^{322,329} for methoxide addition to 5-nitropyrimidine and its 2- and 4-methoxy derivatives. Methoxide addition to 5-nitropyrimidine in dimethyl sulfoxide gives the C-2



³²⁴ C. Abbolito, C. Iavarone, G. Illuminati, F. Stegel, and A. Vazzoler, *J. Am. Chem. Soc.* **91**, 6746 (1969).

³²⁵ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **23**, 957 (1970).

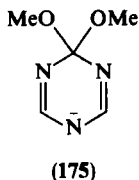
³²⁶ F. Terrier, A. P. Chatrousse, and R. Schaal, *J. Org. Chem.* **37**, 3010 (1972).

³²⁷ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **23**, 963 (1970).

³²⁸ R. Schaal, F. Terrier, J. C. Halle, and A. P. Chatrousse, *Tetrahedron Lett.* p. 1393 (1970).

³²⁹ M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **22**, 2561 (1969).

adduct (172). The 2-methoxy derivative gives the C-4 adduct (173), although a claim for the presence of a very small amount of the C-2 adduct has also been made.³²⁹ Deuterium-labeling studies indicate that 174 is formed from 4-methoxy-5-nitropyrimidine in dimethyl sulfoxide. No σ -complex from 2-methoxypyrimidine is observable even in 10 M NaOMe in dimethyl sulfoxide.³²¹ The reported³²² rapid exchange of the methoxy group of 2-methoxy-1,3,5-triazine in basic methanol presumably proceeds via 175. It



should be noted that the study of Meisenheimer complex formation by all of the above methoxypyridines and methoxypyrimidines is complicated by demethylation reactions which also occur in these strongly basic solutions.^{321,324,329} Such demethylations are slower in dimethyl sulfoxide than in methanol.³²⁴

Methoxide addition in basic methanolic solutions has been reported for various mononitro- and dinitrothiophenes and -selenophenes. The presence of C-2 adducts (177) has been established for each of the thiophenes and selenophenes in Table VIII.³³⁰⁻³³⁶ 2-Nitro-3-methoxythiophene adds methoxide at C-5 in dimethyl sulfoxide to give 178.³³⁰ No adduct could be observed for 2-methyl-5-nitrothiophene under the same conditions.³³⁰

TABLE VIII
FORMATION OF MEISENHEIMER COMPLEXES (177) BY
THIOPHENES AND SELENOPHENES (176) IN METHANOL

X	Y	Z	R	References
S	H	NO ₂	OCH ₃	330
S	NO ₂	NO ₂	OCH ₃	331-335
S	NO ₂ , CN	NO ₂ , CN	H	333, 334
Se	NO ₂ , CN	NO ₂ , CN	H	334
Se	NO ₂	NO ₂	OCH ₃	335, 336

³³⁰ D. Spinelli, V. Armanino, and A. Corrao, *J. Heterocycl. Chem.* **7**, 1441 (1970).

³³¹ G. Doddi, G. Illuminati, and F. Stegel, *J. Chem. Soc., Chem. Commun.* p. 953 (1969).

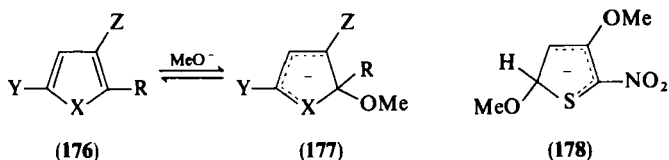
³³² G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.* **36**, 1918 (1971).

³³³ G. Doddi, G. Illuminati, and F. Stegel, *J. Chem. Soc., Chem. Commun.* p. 1143 (1972).

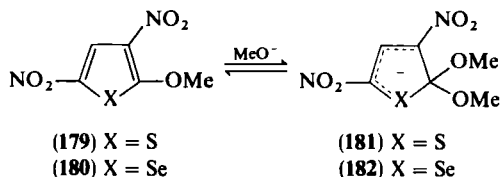
³³⁴ C. Paulmier, M. P. Simonnin, A. P. Chatrousse, and F. Terrier, *Tetrahedron Lett.* p. 1123 (1973).

³³⁵ F. Terrier, A. P. Chatrousse, C. Paulmier, and R. Schaal, *J. Org. Chem.* **40**, 2911 (1975).

³³⁶ F. Terrier, A. P. Chatrousse, R. Schaal, C. Paulmier, and P. Pastour, *Tetrahedron Lett.* p. 1961 (1972).



Terrier *et al.*³³⁵ have made a detailed quantitative study of methoxide addition to 2-methoxy-3,5-dinitrothiophene (**179**) and its selenophene analog



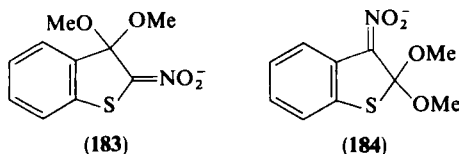
(**180**); pK_a values of 11.36 for formation of **181** and 10.07 for **182** were obtained relative to a standard state of pure methanol. Clearly, this selenophene is somewhat more susceptible to Meisenheimer complex formation than its thiophene analog. Careful kinetic studies in buffered methanol solutions indicated that pseudo-first-order rate constants for formation (k_f) and decomposition (k_d) of the methoxide adducts are described by Eqs. (40) and (41). Activation parameters ($10^\circ\text{--}40^\circ$) for k_{OMe} were: $\Delta H^\ddagger = 9.9 \text{ kcal}$

$$k_f = k_{\text{MeOH}} + k_{\text{OMe}}[\text{MeO}^-] \quad (40)$$

$$k_d = k_1[\text{H}^+] + k_2 \quad (41)$$

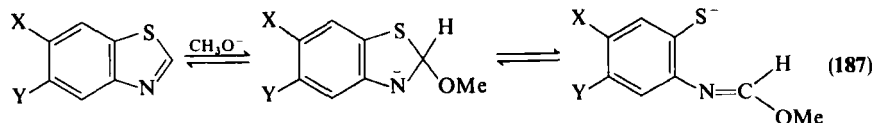
mol^{-1} , $\Delta S^\ddagger = -17.8 \text{ cal mol}^{-1} \text{ deg}^{-1}$ for **179**; $\Delta H^\ddagger = 12.2 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -8.4 \text{ cal mol}^{-1} \text{ deg}^{-1}$ for **180**. The similarity of Eqs. (40) and (41) for Meisenheimer complex formation and Eqs. (26) and (27) for pseudobase formation further demonstrates the close relationship between these reactions. Meisenheimer complex formation is also characterized^{27,326,335} by negative entropies of activation of similar magnitude to those observed⁹² for pseudobase formation.

Methoxide addition has also been reported for two bicyclic heteroaromatic ring systems. 3-Methoxy-2-nitro- and 2-methoxy-3-nitrobenzothiophene add methoxide ion at C-3 and C-2, respectively, to give **183** and **184**. Spectral, equilibrium, and kinetic studies of these reactions have been made.³³⁷



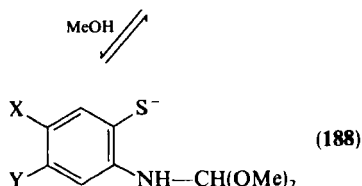
³³⁷ F. DeSantis and F. Stegel, *Gazz. Chim. Ital.* **103**, 649 (1973).

Both 5- and 6-nitro-1,3-benzothiazole (**185** and **186**) add methoxide at C-2; however, these adducts are unstable with respect to a subsequent ring-opening reaction.³³⁸⁻³⁴⁰ As with the benzothiazolium cation (Section V,A), the driving force for the ring-opening reaction is the generation of the



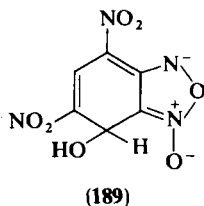
(185) X = H, Y = NO₂

(186) X = NO₂, Y = H



thiolate anions **187** and **188**. The rates of both the methoxide addition and ring-opening steps have been measured for 6-nitro-1,3-benzothiazole in methanol–dimethyl sulfoxide mixtures.³⁴⁰

Considerable work has been done on Meisenheimer complex formation from nitrobenzofuroxans (e.g., **189**) and nitrobenzofurazans;^{27,341-345} however, since these reactions involve nucleophilic attack in the homocyclic ring, they will not be considered further in the present work.



Quantitative studies of rates and equilibria for formation of heterocyclic Meisenheimer complexes are summarized in Table IX. Association constants are defined by Eq. (42)

$$K = [\text{complex}]/[\text{aromatic}][\text{RO}^-] \quad (42)$$

³³⁸ G. Bartoli, G. B. Fiorentino, F. Ciminale, and P. E. Todesco, *J. Chem. Soc., Chem. Commun.* p. 732 (1974).

³³⁹ G. Bartoli, F. Ciminale, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 2* p. 1472 (1975).

³⁴⁰ G. Bartoli, M. Lelli, F. Ciminale, and O. Attanasi, *J. Chem. Soc., Perkin Trans. 2* p. 20 (1977).

³⁴¹ A. J. Boulton and D. P. Clifford, *J. Chem. Soc.* p. 5414 (1965).

³⁴² N. E. Brown and R. T. Keyes, *J. Org. Chem.* **30**, 2452 (1965).

³⁴³ P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.* **11**, 305 (1968).

³⁴⁴ W. P. Norris and J. Osmundsen, *J. Org. Chem.* **30**, 2407 (1965).

³⁴⁵ F. Terrier, F. Millot, and W. P. Norris, *Bull. Soc. Chim. Fr.* p. 551 (1975).

TABLE IX
RATE AND EQUILIBRIUM CONSTANTS FOR FORMATION OF HETEROCYCLIC MEISENHEIMER COMPLEXES^a

Heterocycle	K (M^{-1})	k_{OMc} ($M^{-1} \text{ sec}^{-1}$)	k_2 (sec^{-1})	Conditions	Reference	References to further data
2,4-Dinitrothiophene	800	15	0.019	MeOH, 25°	333	
2-Methoxy-3,5-dinitrothiophene	3×10^{5b}	27.2	7.8×10^{-5}	MeOH, 20°	335	332, 333, 335
2-Methoxy-3,5-dinitroselenophene	6×10^{6c}	70	1.04×10^{-5}	MeOH, 20°	335	335, 336
3,5-Dinitropyridine	16.6	33.2 ^d	2	H ₂ O, 20°	328	328
	72.5	1740	24	MeOH, 20°	328	328
2-Methoxy-3,5-dinitropyridine	1.91			MeOH, 20°	324	
4-Methoxy-3,5-dinitropyridine	2870 ^e	16.5	5.76×10^{-3}	MeOH, 20°	326	321, 323, 326
	11 ^f	275	25	MeOH, 20°	326	326
2-Methoxy-5-nitropyrimidine	~2-3			Me ₂ SO, 27°	329	
4-Methoxy-5-nitropyrimidine	~2-3			Me ₂ SO, 27°	329	
2-Methoxy-3-nitrobenzothiophene	370	0.215	5.8×10^{-4}	MeOH, 25°	337	
2-Nitro-3-methoxybenzothiophene	600	0.047	7.5×10^{-5}	MeOH, 25°	337	
6-Nitrobenzothiazole	2.77	30	11	MeOH/Me ₂ SO = 30:70, 25°	340	340

^a Rate and equilibrium constants are defined by Eqs. (40), (41), and (42).

^b $k_{CH_3OH} = 10^{-7} \text{ sec}^{-1}$, $k_1 = 1.05 \times 10^4 M^{-1} \text{ sec}^{-1}$.

^c $k_{CH_3OH} = 5.75 \times 10^{-7} \text{ sec}^{-1}$, $k_1 = 2.65 \times 10^3 M^{-1} \text{ sec}^{-1}$.

^d $k_{OH\cdot}$.

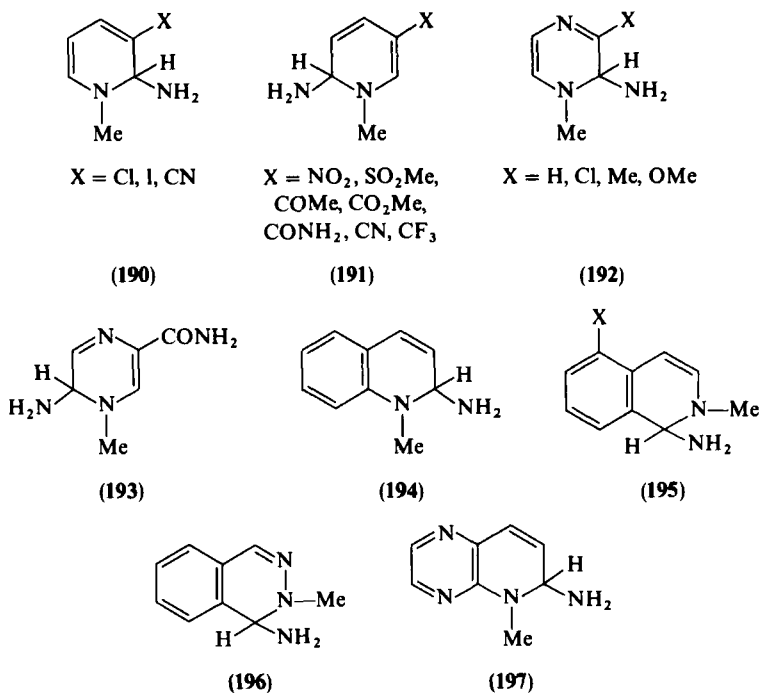
^e C-4 σ -complex.

^f C-2 σ -complex.

C. PSEUDOBASES IN LIQUID AMMONIA

The formation of σ -complexes in liquid ammonia solutions has been observed for both heteroaromatic cations and neutral heteroaromatic molecules. These σ -complexes arise via addition of the amide ion to the heterocycle and are exactly analogous to the pseudobases and Meisenheimer complexes of aqueous and alcoholic media.

Zoltewicz and co-workers³⁴⁶⁻³⁴⁹ have shown on the basis of PMR spectral studies that a wide range of nitrogen heteroaromatic cations exist as their pseudobases (e.g., 190-197) in liquid ammonia free of added amide ion. In all cases the PMR spectra of the amide adducts are exactly analogous to those of the corresponding methoxide adducts in methanol.²⁶



The equilibria between cation and pseudobase are established rapidly at temperatures above -50° , and in each of the cases (190-197), the equilibrium lies heavily in favor of the pseudobase. An enhanced stability of pseudobase relative to the cation is quite apparent in liquid ammonia

³⁴⁶ J. A. Zoltewicz and J. K. O'Halloran, *J. Am. Chem. Soc.* **97**, 5531 (1975).

³⁴⁷ J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.* **41**, 1303 (1976).

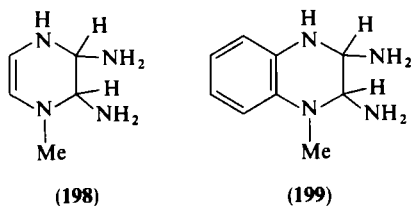
³⁴⁸ J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.* **41**, 1308 (1976).

³⁴⁹ J. A. Zoltewicz, T. M. Oestreich, J. K. O'Halloran, and L. A. Helmick, *J. Org. Chem.* **38**, 1949 (1973).

relative to the observed stabilities in aqueous or alcoholic solutions. Of **190**–**197**, only the pseudobase corresponding to **197** is formed readily in neutral aqueous solutions. Some of this difference in the position of equilibrium between pseudobase and cation can certainly be traced to the differing abilities of ammonia and hydroxylic solvents to solvate the species involved in the equilibrium.³⁴⁹ However, the much greater nucleophilicity of ammonia than of water (and of amide ion than of hydroxide ion) is probably the major factor favoring pseudobase formation in ammonia relative to water.

Pyridinium cations bearing strongly electron-withdrawing substituents on C-3 undergo predominant nucleophilic attack at C-6 to give **191**, whereas the 3-halopyridinium ions preferentially produce the C-2 adducts (**190**).^{347,349} The 1-methyl-3-cyanopyridinium cation gives a mixture of the C-2 and C-6 amide adducts at -40° ,³⁴⁷ and this suggests that steric effects from the C-3 substituent as well as electronic effects may be important in determining the equilibrium between the C-2 and C-6 adducts. Neither the 1-methyl nor 1-benzyl pyridinium cations undergo detectable pseudobase formation in neutral ammonia. However, addition of potassium hydroxide produces the C-2 adducts in these cases.³⁴⁷ The 1-methoxypyridinium cation is completely converted to the C-2 pseudobase at -50° in ammonia free of added base; however, in general, such 1-methoxypyridinium cations undergo further reactions to produce ring-opened products in these media.³⁴⁷

The substituent effects noted above for 3-substituted pyridinium ions also seem to apply to 3-substituted pyrazinium cations (see **192** and **193**).³⁴⁷ The 1-methylpyrazinium cation is completely converted into **192** ($X = H$) at -50° ; however, as the temperature is increased, the covalent ammonate **198** of **192** ($X = H$) becomes the predominant species present.³⁴⁷ The diadduct

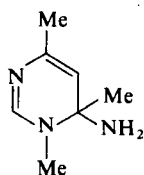


199 is also the predominant species present in solutions of the 1-methylquinoxalinium cation in liquid ammonia. The species **199** is exactly analogous to the covalent hydrate **12** of the pseudobase of the 1-methylquinoxalinium cation in aqueous solution (Section II).

Several *N*-methylpyrimidinium cations have been observed to form C-6 pseudobases in liquid ammonia.³⁵⁰ Interestingly, the presence of a methyl

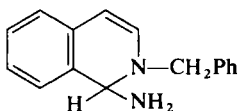
³⁵⁰ E. A. Oestveen, H. C. van der Plas, and H. Jongejan, *Recl. Trav. Chim. Pays-Bas* **93**, 114 (1974).

group at C-6 does not change the site of nucleophilic attack in the case of the 1,4,6-trimethylpyrimidinium cation which gives the pseudobase **200**.



(200)

Zoltewicz and O'Halloran³⁴⁶ have used the observed nonequivalence of the methylene protons in *N*-benzyl isoquinoline pseudobases (**201**) to study the rates of exchange of the C-1 amino group with solvent. The diastereo-



(201)

topicity of the methylene protons of **201** arises from the chirality of the C-1 atom. The signals of these protons occur as an AB pair of doublets at low temperatures; however, at higher temperatures the signals coalesce to a singlet. This coalescence temperature decreases with increasing ammonium ion (NH_4^+) concentration, and this indicates that amino group exchange with solvent is catalyzed by ammonium ion. Measurements of coalescence temperatures and the temperature dependence of ammonium ion catalysis allows the determination of the relative rates (k_{rel}) of amino group exchange. For the 5-substituted isoquinolines, k_{rel} are reasonably well correlated ($r = 0.96$) by the Hammett σ_m -constants for the 5-substituents:

$$\log k_{\text{rel}} = -1.85 \sigma_m + 0.1$$

A better correlation ($r = 0.994$) is obtained using separate inductive and resonance parameters for the 5-substituents [Eq. (43)]. These substituent

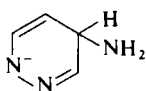
$$\log k_{\text{rel}} = -1.74 \sigma_I - 0.41 \sigma_R^+ - 0.01 \quad (43)$$

effects indicate some production of positive charge in the isoquinoline moiety in the rate-determining transition state. The exchange mechanism most likely involves dissociation to form the isoquinolinium cation followed by re-addition of ammonia (an $\text{S}_{\text{N}}1$ process), although an $\text{S}_{\text{N}}2$ displacement cannot be ruled out at present.³⁴⁶

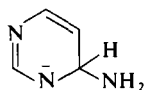
PMR spectral studies may also be conveniently used to investigate the addition of a wide range of other nucleophiles to heteroaromatic cations in

liquid ammonia. Data are available for the addition of the nitromethyl carbanion and ethanethiolate anion to a variety of pyridinium, pyrazinium, isoquinolinium, and phthalazinium cations.³⁴⁸

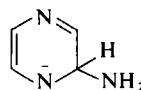
Many neutral heteroaromatic molecules have been shown to form anionic amino σ -complexes in liquid ammonia in the presence of the amide anion. While no PMR spectral evidence could be obtained for an adduct between pyridine and amide ion in liquid ammonia, the monocyclic diazines do readily form σ -complexes.³⁵¹ Thus, pyridazine, pyrimidine, and pyrazine generate the adducts **202**–**204**, respectively. Several unidentified weak signals in the PMR spectra of **202** and **203** suggest the possibility of the presence of minor amounts of other adducts as well. For these diazines, $K > 10^5 M^{-1}$



(202)



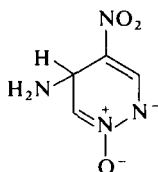
(203)



(204)

has been estimated for liquid ammonia solutions at 25°. Similar adducts have also been reported for various substituted pyridazines and their *N*-oxides,⁵⁹ pyrimidines,^{58,352,353} and pyrazines;³⁵⁴ and ¹³C-NMR spectroscopy has also been shown to be useful for the study of such σ -complexes.^{58,59}

4-Nitropyridazine *N*-oxides readily form σ -complexes (e.g., **205**) in liquid ammonia in the absence of free amide ion.³⁵⁵ The activating effect of the



(205)

nitro group with respect to nucleophilic attack is clear in these systems since pyridazine *N*-oxides lacking a 4-nitro substituent do not form σ -complexes under these conditions.

³⁵¹ J. A. Zoltewicz and L. M. Helmick, *J. Am. Chem. Soc.* **94**, 682 (1972).

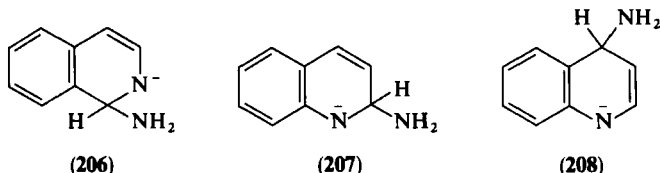
³⁵² J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **93**, 231 (1974).

³⁵³ J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **92**, 1232 (1973).

³⁵⁴ P. J. Lont, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **92**, 708 (1973).

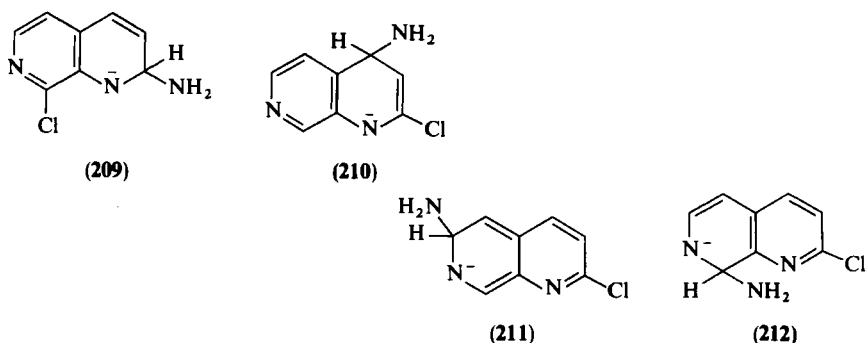
³⁵⁵ D. E. Klinge and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **94**, 233 (1975).

Isoquinoline readily adds amide ion in liquid ammonia to give the C-1 adduct (**206**).³⁵⁶ The addition of amide ion to quinoline is interesting in that, whereas the C-2 adduct (**207**) is the kinetically controlled product, the C-4



adduct (**208**) appears to be thermodynamically more stable.¹⁴ The conversion of **207** into **208** can be conveniently monitored by PMR spectroscopy in liquid ammonia at -45° .

Van der Plas *et al.*³⁵⁷ have studied amide ion addition to 2-chloro- and 8-chloro-1,7-naphthyridines in liquid ammonia at -50° . Whereas the 8-chloro isomer clearly gives the C-2 adduct (**209**), the 2-chloro isomer gives a mixture of the C-4, C-6, and C-8 adducts (**210–212**) in the ratio 4.25:1:1.75 under these conditions.



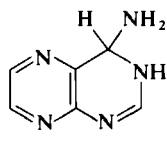
Pteridine in liquid ammonia at -40° gives a mixture of the mono- and bisammonates (**213** and **214**) which consists of 60% **214** and 40% **213** at equilibrium.³⁵⁸ Higher temperatures more heavily favor the bis-adduct at equilibrium. Substituted pteridines behave similarly. These results are exactly analogous to the formation of mono- and bis-covalent hydrates by the pteridine cation in aqueous acid.³⁵⁹

³⁵⁶ J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, *J. Org. Chem.* **38**, 1947 (1973).

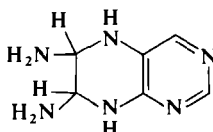
³⁵⁷ H. C. van der Plas, M. Wozniak, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **95**, 151 (1977).

³⁵⁸ A. Nagel, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **94**, 45 (1975).

³⁵⁹ A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc. B* p. 1105 (1966).

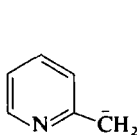


(213)

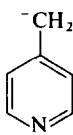


(214)

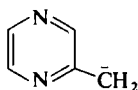
Anion formation via deprotonation reactions (e.g., **215**–**219**) takes preference over σ -complex formation for appropriate alkyl-³⁶⁰ and amino-substituted^{352,353} heteroaromatics. 5-Bromo-4-methylpyrimidine is reported³⁵² to give a 1:3 ratio of adduct (**220**) to anhydrobase (**221**) at -55° .



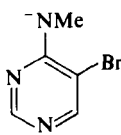
(215)



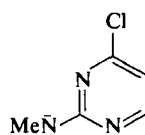
(216)



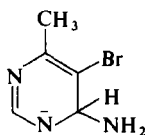
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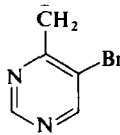
(218)



(219)



(220)



(221)

VII. Pseudobases of Metal Complexes Containing Heterocyclic Ligands

Over the past few years, Gillard *et al.*^{361–369} have presented evidence that complexation of 2,2'-dipyridyl and 1,10-phenanthroline and their

³⁶⁰ J. A. Zoltewicz and L. S. Helmick, *J. Org. Chem.* **38**, 658 (1973).

³⁶¹ R. D. Gillard and J. R. Lyons, *J. Chem. Soc., Chem. Commun.* p. 585 (1973).

³⁶² R. D. Gillard, *Inorg. Chim. Acta* **11**, L21 (1974).

³⁶³ R. D. Gillard, *Coord. Chem. Rev.* **16**, 67 (1975).

³⁶⁴ R. D. Gillard, C. T. Hughes, and P. A. Williams, *Transition Met. Chem.* **1**, 51 (1976).

³⁶⁵ R. D. Gillard, L. A. P. Kane-Maguire, and P. A. Williams, *J. Chem. Soc., Dalton Trans.* p. 1039 (1977).

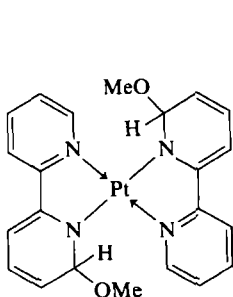
³⁶⁶ R. D. Gillard, L. A. P. Kane-Maguire, and P. A. Williams, *Transition Met. Chem.* **2**, 12 (1977).

³⁶⁷ R. D. Gillard and P. A. Williams, *Transition Met. Chem.* **2**, 14 (1977).

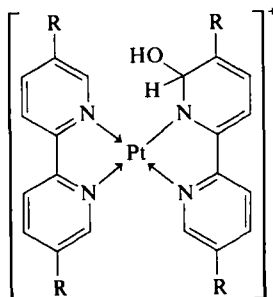
³⁶⁸ K. H. Al-Obaidi, R. D. Gillard, L. A. P. Kane-Maguire, and P. A. Williams, *Transition Met. Chem.* **2**, 64 (1977).

³⁶⁹ E. Bielli, R. D. Gillard, and D. W. James, *J. Chem. Soc., Dalton Trans.* p. 1837 (1976).

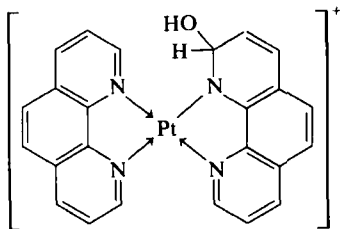
substituted derivatives with various metal ions activates these heterocycles toward nucleophilic addition at ring carbon atoms. PMR spectral data of various degrees of reliability have been interpreted in terms of the formation of the pseudobases (222–225) for a number of metal complexes. The



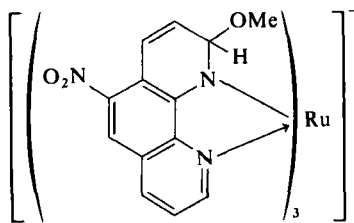
(222)



(223) R = H, Me



(224)



(225)

electronic absorption spectra of such metal complexes display a pH dependence consistent with pseudobase formation. Similar spectral data indicate analogous cyanide σ -complexes are also formed by some of these metal complexes.^{370,371}

Quantitative rate and equilibrium studies for pseudobase formation by metal complexes are summarized in Table X. Activation parameters for methoxide ion addition to $\text{Ru}(5\text{-nitro-1,10-phenanthroline})_3^{2+}$ are $\Delta H^\ddagger = 10.6 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -10 \text{ cal mol}^{-1} \text{ deg}^{-1}$ and for ethoxide ion addition to the same metal complex are $\Delta H^\ddagger = 11.1 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -6.9 \text{ cal mol}^{-1} \text{ deg}^{-1}$.³⁶⁵

³⁷⁰ R. D. Gillard, C. T. Hughes, L. A. P. Kane-Maguire, and P. A. Williams, *Transition Met. Chem.* 1, 114 (1976).

³⁷¹ R. D. Gillard, C. T. Hughes, L. A. P. Kane-Maguire, and P. A. Williams, *Transition Met. Chem.* 1, 226 (1976).

TABLE X
QUANTITATIVE DATA FOR PSEUDOBASE FORMATION BY METAL COMPLEXES HAVING HETEROCYCLIC LIGANDS

Reaction	L ^a	M	pK _R	k _{OH} (M ⁻¹ sec ⁻¹)	k ₂ (sec ⁻¹)	Conditions	Reference
ML ₃ ²⁺ $\xrightleftharpoons{OH^-}$ ML ₂ (LOH) ⁺	A	Fe	12.9			H ₂ O, 0°	364
		Fe	12.1	7.14	0.23	H ₂ O, 37°	364
		Ru	11.4	18.9	0.13	H ₂ O, 37°	364
ML ₂ ²⁺ $\xrightleftharpoons{OH^-}$ ML(LOH) ⁺	B	Pt	~11.5			H ₂ O	369
		Pt	9.0			H ₂ O	361
		Pt	9.5			H ₂ O	361
		Pd	8.2			H ₂ O	361
ML ₃ ²⁺ $\xrightleftharpoons{MeO^-}$ ML ₂ (LOMe) ⁺	A	Ru	62 ^b	99 ^c	1.6	MeOH, 0.1° ^e	365
			40 ^b	608 ^c	15.1	MeOH, 25.8°	365
ML ₃ ²⁺ $\xrightleftharpoons{EtO^-}$ ML ₂ (LOEt) ⁺	A	Ru	>250 ^b	650 ^d		EtOH, 4.2° ^e	365
				4770 ^d		EtOH, 31.3°	365

^a A = 5-Nitro-1,10-phenanthroline; B = 1,10-phenanthroline; C = 2,2'-dipyridyl; D = 5,5'-dimethyl-2,2'-dipyridyl.

^b K (M⁻¹).

^c k_{OMe}.

^d k_{OEt}.

^e Also data at intermediate temperatures.

The divalent metal ion complexes of 2,2'-dipyridyl and 1,10-phenanthroline derivatives are much more susceptible to pseudobase formation than the corresponding *N*-alkyl quaternary cations. Thus, $pK_{R^+} > 14$ for pseudobase formation by the *N*-methyl monocations of both 2,2'-dipyridyl and 1,10-phenanthroline,⁴⁶ whereas the Pt^{2+} complexes of these heterocycles have pK_{R^+} values of 9.0 and ~ 11.5 , respectively.^{361,369} This latter value indicates that $Pt(1,10\text{-phenanthroline})_2^{2+}$ is less susceptible to pseudobase formation than the 1,10-phenanthrolinium dications **17** ($pK_{R^+} = 9.54$) and **18** ($pK_{R^+} = 9.17$).⁴⁶

4-Thiazolidinones

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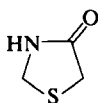
Sambalpur University, Jyoti Vihar, Burla, Sambalpur, Orissa, India

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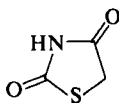
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I. Introduction

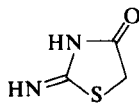
The chemistry of 4-thiazolidinones (**1**) was reviewed in depth by Brown in 1962.¹ Since then, largely due to the wide variety of physiological activity demonstrated by this class of compounds, several thousand papers² on the chemistry of 4-thiazolidinone derivatives, exclusive of rhodanine derivatives, have been published. This review will consider only the important literature highlights of **1**, 2,4-thiazolidinediones (**2**), 2-imino-4-thiazolidinones (**3**), and 4-oxo-2-thiazolin-2-ylhydrazones (**4**). Neither rhodanine (**5**) nor the extensive patent and obscure literature references dealing with 4-thiazolidinones will be considered in any detail within this review.



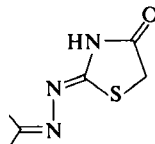
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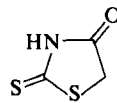
(2)



(3)



(4)



(5)

II. Synthetic Aspects: An Overview

The most widely used procedures for the preparation of 4-thiazolidinones describe the formation of the 3,4-bond via cyclization of an appropriately substituted acyclic compound which had been generally prepared from either thiourea or thioglycolic (mercaptoacetic) acid derivatives. Formation of

¹ F. C. Brown, *Chem. Rev.* **61**, 463 (1961).

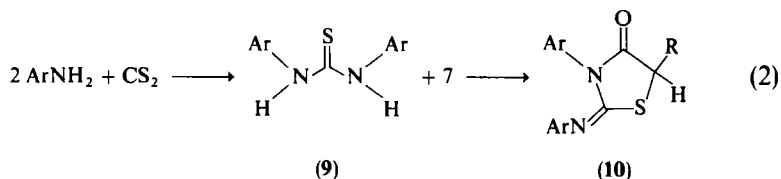
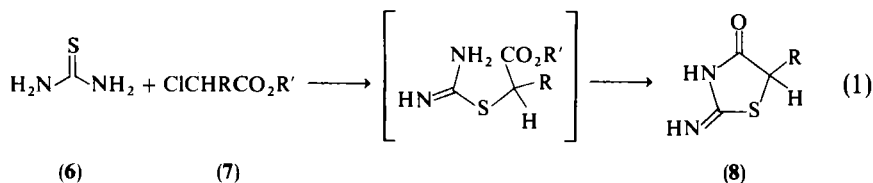
² M. S. Raasch, *J. Heterocycl. Chem.* **11**, 587 (1974).

the ring from other fragments, chemical transformations of related heterocyclic systems, and rearrangements of isomers to the appropriate 4-thiazolidinone skeleton comprise minor synthetic procedures.

A. CYCLIZATION PROCEDURES

1. Formation of the 3,4-Bond

The simplest synthesis of pseudothiohydantoin (**8**) is by condensation of thiourea (**6**) with substituted α -chloroacetates (**7**)³⁻⁵ [Eq. (1)]. Synthons⁶ of **7**, epoxyacids,⁷ α -chloroacetic anhydrides,⁸ and dialkyl acetylenedicarboxylate,⁹ have been successfully substituted for **7**. Symmetrical diarylthioureas (**9**), conveniently synthesized from the corresponding arylamine and carbon disulfide, react with α -haloacetic acid derivatives to give a single thiazolidinone **10**^{8,10,11} [Eq. (2)].



³ M. Hauser, *J. Org. Chem.* **27**, 43 (1962).

⁴ H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.* p. 1022 (1963).

⁵ M. R. Udupa and M. Padmanabhan, *J. Inorg. Nucl. Chem.* **37**, 1808 (1975).

⁶ W. Reeve and M. Nees, *J. Am. Chem. Soc.* **89**, 647 (1967).

⁷ A. S. U. Choughuley and M. S. Chadha, *Indian J. Chem.* **1**, 437 (1963).

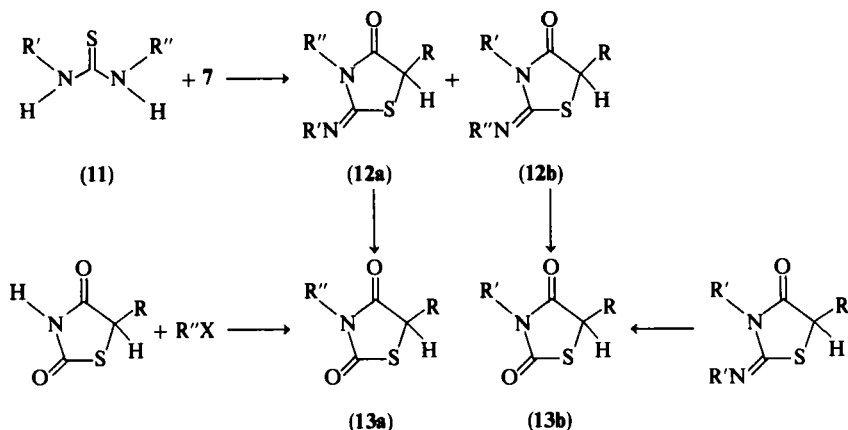
⁸ Yu V. Svetkin, Kh. F. Bikbaeva, R. R. Faizulov, and A. N. Glazev, *Zh. Obshch. Khim.* **42**, 2055 (1972).

⁹ H. Nagase, *Chem. Pharm. Bull.* **21**, 270 and 279 (1973).

¹⁰ R. P. Rao, *J. Indian Chem. Soc.* **38**, 787 (1961); R. P. Rao and S. R. Singh, *ibid.* **50**, 492 (1973); S. R. Singh, *ibid.* **53**, 595 (1976); S. Giri and S. C. Shukla, *Indian J. Appl. Chem.* **31**, 202 (1968).

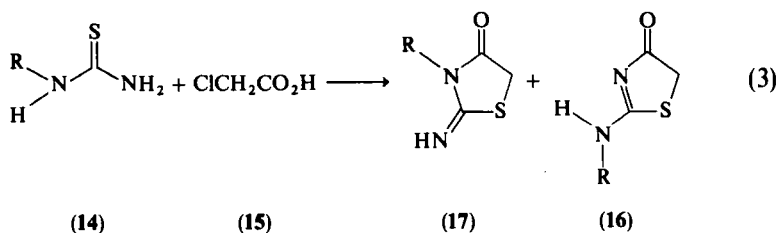
¹¹ N. C. Misra and K. K. Patnaik, *Indian J. Appl. Chem.* **34**, 148 (1971).

Symmetrical dialkylthioureas react with **7** to give a single product. Unsymmetrical substituted thioureas (**11**) have been condensed with **7** to afford two isomeric 2-imino-4-thiazolidinones (**12a,b**); however in most cases, a predominant isomer has been obtained. Structural configurations of **12** have been deduced by hydrolysis to the corresponding diones (**13a,b**),



SCHEME 1

respectively, shown in Scheme 1. Independent synthesis of **13a** and **b** can be accomplished from the sym-disubstituted thioureas, followed by hydrolysis, or in limited cases, by alkylation of **1**. Possibilities of prior or subsequent isomerization of benzyl derivatives under severe hydrolysis conditions have been noted.^{12,13} Reaction conditions can also greatly influence the product distribution.¹⁴ *N*-Alkylthioureas (**14**) react with chloroacetic acid (**15**) at



100° in the presence of sodium acetate to give 2-alkylaminothiazolin-4-one (**16**) and traces of **17** [Eq. (3)] whereas, at 50° in the absence of base, *N*-methylthiourea (**14**; R = Me) with **15** gives **17** as the major product along

¹² Yu. A. Baskakov, L. L. Volovnik, A. F. Vasil'ev, N. L. Aryutkina, and V. V. Negrebetskii, *Khim. Geterotsikl. Soedin.* p. 1481 (1970).

¹³ S. P. Kharidia, B. K. Raval, and J. J. Trivedi, *J. Indian Chem. Soc.* **39**, 43 (1962).

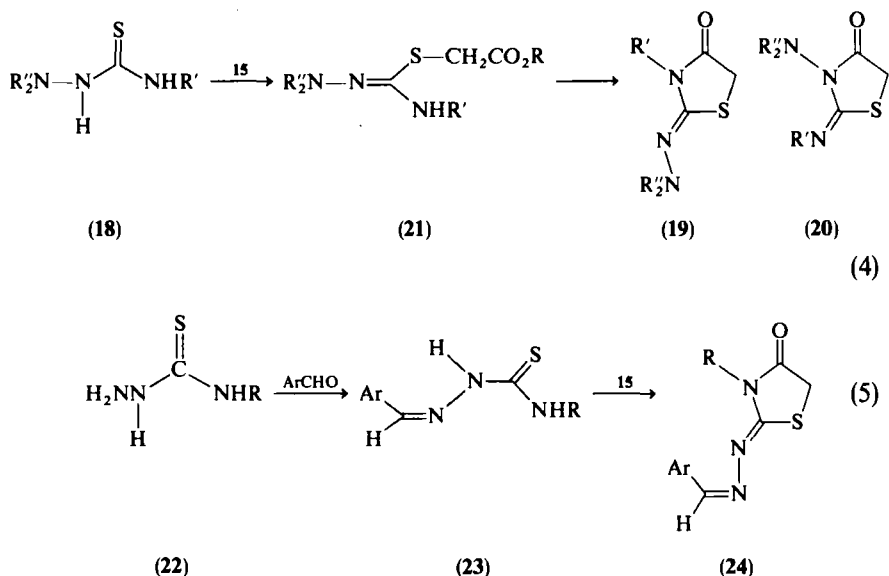
¹⁴ E. Akerblom, *Acta Chem. Scand.* **21**, 843 (1967).

with traces of **16**.¹⁴ Whereas primary *N*-alkylthioureas can give both **16** and **17**, secondary *N*-alkylthioureas afford exclusively **16**.¹⁴

α -Haloacetic acid derivatives have been successfully reacted with *N*-alkyl-,¹⁴⁻¹⁷ *N*-aryl-,¹⁸⁻²³ *N*-heteroaryl-,^{24,25} *N,N'*-dialkyl (sym and unsym)-,²⁶ *N,N'*-diaryl (sym)-,^{8-11,26} *N,N'*-diaryl (unsym)-,²⁶⁻³⁰ *N*-alkyl-*N'*-aryl-,^{13,17,26,31-36} *N*-alkyl-*N'*-heteroaryl-,³⁶ and *N*-aryl-*N'*-heteroaryl³⁷⁻⁴² thioureas.

- ¹⁵ M. L. Vasa, J. J. Trivedi, and K. C. Kshatriya, *J. Indian Chem. Soc.* **36**, 648 (1959).
¹⁶ H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.* p. 1018 (1963).
¹⁷ P. N. Dhal, T. E. Achary, and A. Nayak, *Indian J. Chem.* **13**, 753 (1975).
¹⁸ B. K. Ravel and J. J. Trivedi, *J. Indian Chem. Soc.* **37**, 435 (1960); **39**, 47 (1962).
¹⁹ K. C. Joshi and S. C. Bahel, *J. Indian Chem. Soc.* **39**, 121 (1962).
²⁰ H. K. Pujari, *J. Indian Chem. Soc.* **43**, 657 (1966); H. S. Chaudhary and H. K. Pujari, *Indian J. Chem.* **6**, 488 (1968); V. K. Chadha, C. S. Panda, and H. K. Pujari, *ibid.* **9**, 910 (1971).
²¹ Yu. V. Svetkin, A. N. Minlibaeva, and S. A. Vasil'eva, *Zh. Obshch. Khim.* **38**, 116 (1968).
²² T. E. Acharya, P. N. Dhal, and A. Nayak, *J. Inst. Chem., Calcutta* **44**, 166 (1972); T. E. Achary, C. S. Panda, and A. Nayak, *J. Indian Chem. Soc.* **52**, 1065 (1975).
²³ O. V. Vladimirska, *Farm. Zh. (Kiev)* **18**, 7 (1963); *Chem. Abstr.* **60**, 4126 (1963).
²⁴ T. E. Achary and A. Nayak, *Curr. Sci.* **41**, 539 (1972); P. N. Dhal and A. Nayak, *J. Inst. Chem., Calcutta* **45**, 127 (1973); P. N. Dhal, T. E. Achary, A. Nayak, and M. K. Rout, *J. Indian Chem. Soc.* **50**, 680 (1973); P. N. Dhal, T. E. Achary, and A. Nayak, *ibid.* **51**, 931 (1974).
²⁵ R. Shyam and I. C. Tiwari, *Agric. Biol. Chem.* **39**, 715 (1975).
²⁶ J. P. Trivedi, S. J. Contractor, and I. D. Shah, *J. Indian Chem. Soc.* **43**, 265 (1966).
²⁷ K. S. L. Srivastava, *Indian J. Appl. Chem.* **32**, 369 (1969); *Curr. Sci.* **37**, 315 (1968).
²⁸ R. P. Rao, *J. Indian Chem. Soc.* **48**, 253 (1971).
²⁹ H. N. Pandey and V. J. Ram, *J. Indian Chem. Soc.* **49**, 171 (1972); V. J. Ram, H. N. Pandey, and S. N. Singh, *ibid.* p. 181.
³⁰ S. R. Singh, *J. Indian Chem. Soc.* **52**, 734 (1975).
³¹ M. O. Lozinskii, T. N. Soroka, D. F. Yavorskii, S. S. Kirienko, V. Ya. Yakovleva, and P. S. Pel'kis, *Khim. Geterotsikl. Soedin.* **5**, 501 (1969).
³² S. S. Parmar, C. Dwivedi, A. Chaudhari, and T. K. Gupta, *J. Med. Chem.* **15**, 99 (1972); C. Dwivedi, T. K. Gupta, and S. S. Parmar, *ibid.* p. 553; S. K. Chaudhari, M. Verma, A. K. Chaturvedi, and S. S. Parmar, *J. Pharm. Sci.* **64**, 614 (1975).
³³ K. F. Modi and J. J. Trivedi, *J. Indian Chem. Soc.* **50**, 564 (1973).
³⁴ A.-M. M. E. Omar, *Pharmazie* **28**, 110 (1973).
³⁵ S. M. Ramsh, G. S. Antonova, A. I. Ginak, and E. G. Sochilin, *Zh. Org. Khim.* **11**, 1755 (1975).
³⁶ V. N. Choubey and H. Singh, *Bull. Chem. Soc. Jpn.* **43**, 2233 (1970).
³⁷ P. N. Bhargava and G. C. Singh, *J. Indian Chem. Soc.* **45**, 32 (1968).
³⁸ P. Ram, K. S. L. Srivastava, R. Lakhani, and M. R. Chaurasia, *Indian J. Appl. Chem.* **32**, 279 (1969).
³⁹ S. C. Sharma, *Bull. Chem. Soc. Jpn.* **40**, 2422 (1967).
⁴⁰ E. V. Vladimirskaia, *Zh. Obshch. Khim.* **34**, 2774 (1964).
⁴¹ A. Chaudhary, S. S. Parmar, S. K. Chaudhary, A. K. Chaturvedi, and B. V. Ramsastry, *J. Pharm. Sci.* **65**, 443 (1976).
⁴² P. N. Bhargava and J. Singh, *Curr. Sci.* **41**, 636 (1972).

1,1-Dialkyl-4-arylthiosemicarbazides (**18**) have been condensed with **15** to give the 2-dialkylamino derivatives (**19**),⁴³ as based on its smooth hydrolysis to **2** ($R' = \text{Ph}$) and not the isomeric thiohydantoin (**20**). The intermediary *S*-carboxy (alkyl) isothiosemicarbazides (**21**) have been successfully isolated and subsequently cyclized [Eq. (4)].⁴⁴ Substitution with related heterocyclic rings,⁴⁴ such as the 4-(1,2,4-triazolyl) moiety,^{45,46} can be incorporated from the appropriate *N*-aminoheterocycles. 4-Alkyl (or aryl) thiosemicarbazones (**23**) prepared from the substituted thiosemicarbazide **22** and the desired aldehyde or ketone have been reacted with **15** to give the 2-ylhydrazones **24** [Eq. (5)].⁴⁷⁻⁵⁴



⁴³ F. E. Condon and J. P. Trivedi, *J. Indian Chem. Soc.* **48**, 597 (1971).

⁴⁴ E. Bulka, H. Beyer, and H. Zöllner, *Chem. Ber.* **96**, 1986 (1963).

⁴⁵ M. S. Solanki and J. P. Trivedi, *J. Indian Chem. Soc.* **42**, 817 (1965).

⁴⁶ A. Andolsek, B. Stanovnik, M. Tisler, M. Likar, and P. Schauer, *J. Med. Chem.* **14**, 53 (1971).

⁴⁷ F. Knotz, *Monatsh. Chem.* **93**, 1303 (1962).

⁴⁸ J. P. Trivedi and I. D. Shah, *J. Indian Chem. Soc.* **43**, 275 (1966); I. D. Shah and J. P. Trivedi, *ibid.* **41**, 704 (1964); **40**, 889 (1963).

⁴⁹ V. S. Misra and A. Saxena, *J. Prakt. Chem.* [4] **36**, 260 (1967).

⁵⁰ K. C. Joshi and J. S. Gupta, *Indian J. Chem.* **5**, 139 (1967).

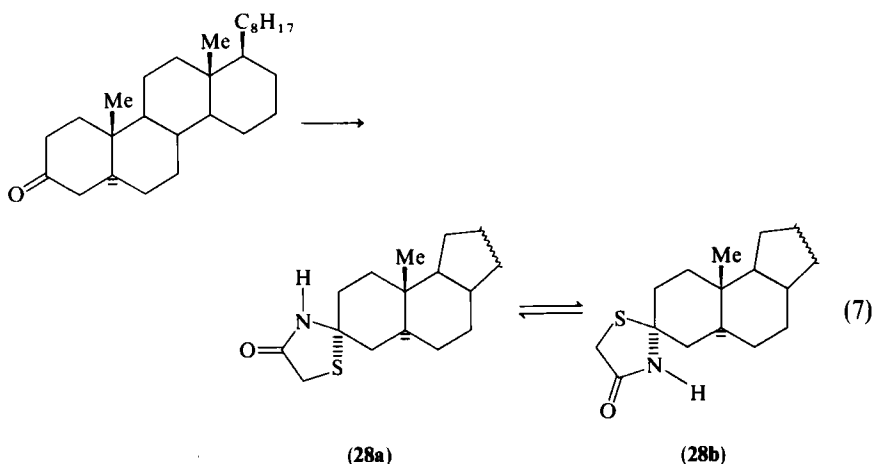
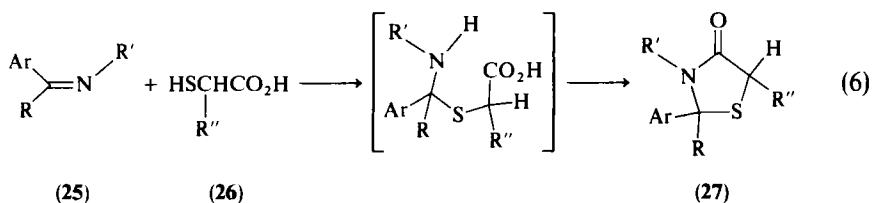
⁵¹ A. F. Pavlenko and S. D. Moshchitskii, *Khim. Geterotsikl. Soedin.* **3**, 259 (1967).

⁵² R. Kumar, T. K. Gupta, and S. S. Parmar, *J. Prakt. Chem.* **312**, 201 (1970).

⁵³ F. D. Popp and E. B. Moynahan, *J. Med. Chem.* **13**, 1020 (1970).

⁵⁴ A. A. Sirotenko and P. A. Ciavarri, *J. Med. Chem.* **9**, 642 (1966).

Aromatic Schiff bases (**25**), usually generated *in situ* from the corresponding aldehyde or ketone and primary amine, undergo a well-known reaction [Eq. (6)] with α -mercaptoalkanoic acids (**26**) or their derivatives to give 4-thiazolidinones (**27**).⁵⁵⁻⁶¹ Preparation of spiro-alicyclic thiazolidinones (**28**) from alicyclic ketones, amines, and primary **26** has been described [Eq. (7)].⁶² Thiazolidinone **28**, when subjected to either acidic or basic conditions, undergoes facile isomerization⁶² similar to the ring-chain tautomeric behavior of imino-thiophenes.⁶³ Polyfluoroacetone imine, unsubstituted on nitrogen, reacts with **26** at 0°–25° under nitrogen to give



⁵⁵ B. K. Ravel and J. J. Trivedi, *J. Indian Chem. Soc.* **37**, 353 (1960).

⁵⁶ R. R. Astik, G. B. Joshi, and K. A. Thaker, *J. Indian Chem. Soc.* **52**, 1071 (1975); **53**, 272 (1976).

⁵⁷ G. Fenech, *Ann. Chim. (Rome)* **50**, 413 (1960).

⁵⁸ J. C. Wilson, R. N. Downer, and H. E. Sheffer, *J. Heterocycl. Chem.* **7**, 955 (1970).

⁵⁹ V. Bellavita and A. Martani, *Gazz. Chim. Ital.* **97**, 135 (1967).

⁶⁰ A. A. Shaiikh, *J. Inst. Chem., Calcutta* **45**, 207 (1973).

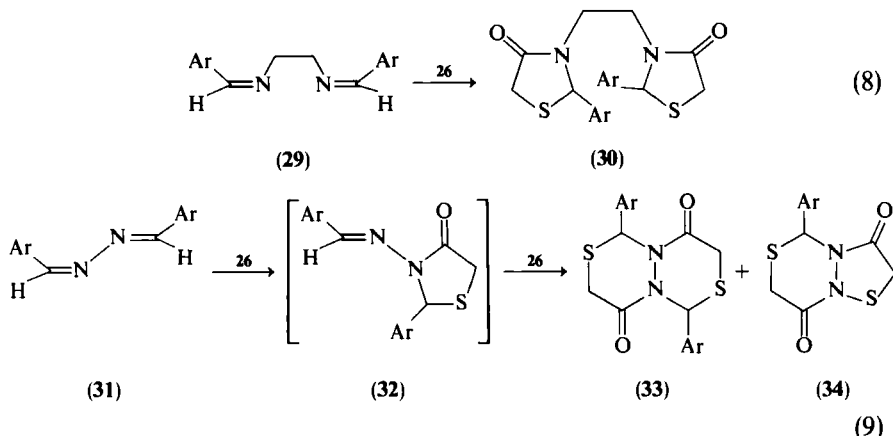
⁶¹ V. G. Barot, P. B. Patel, and J. J. Trivedi, *J. Inst. Chem., Calcutta* **45**, 24 (1973); R. K. Shah and P. B. Patel, *ibid.* **46**, 34 (1974).

⁶² Z. Paryzek and M. Kielczewski, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.* **23**, 91 (1975).

⁶³ G. W. Stacy and P. L. Strong, *J. Org. Chem.* **32**, 1487 (1967).

fluorinated 4-thiazolidinones, whereas *N*-substituted imines react only at increased temperatures.^{2,64} β -Aryl- α -mercaptoacrylic acids easily add to carbon-nitrogen double bonds to generate the 5-arylidene derivatives.^{65,66}

Bis-imines **29** similarly react [Eq. (8)] with **26** to give both the *dl*- and *meso*- forms of 1,2-bis(2-phenylthiazolidin-4-on-3-yl)ethane (**30**).⁶⁷ Azine **31**, however, when reacted with excess **26** at 100°, gives a proposed intermediate (**32**) which undergoes ring opening, followed by addition of a second mole of **26**, to afford **33** and (by oxidation) **34** [Eq. (9)].⁶⁸



Similar to thiol addition to imines, imidic esters,^{69,70} and cyano compounds possessing an α -proton (**35**), such as cyanic acid,⁷¹ cyanamide,⁷¹ monosubstituted cyanimides,⁷² and α -substituted acetonitriles,^{69,70,73,74} react smoothly with α -mercaptoacetic acids (**26**) to generate an unstable acyclic intermediate **36**, which cyclizes to give **37** ($Y = \text{O}, \text{NH}, \text{NR},$ and $\text{CHR},$ respectively) [Eq. (10)].

⁶⁴ N. Ishikawa and T. Kitazume, *Bull. Chem. Soc. Jpn.* **46**, 3260 (1973).

⁶⁵ A. H. Harhash, M. H. Elnagdi, and S. O. Abdallah, *Indian J. Chem.* **11**, 128 (1973).

⁶⁶ J. R. Merchant and B. B. Lakhani, *Curr. Sci.* **45**, 136 (1976).

⁶⁷ L. De Bellis, A. Farina, G. A. Porcelli, and M. L. Stein, *Ric. Sci., Parte 2: Sez. B* **4**, 589 (1964); *Chem. Abstr.* **63**, 1780 (1965).

⁶⁸ G. Fenech and M. Basile, *Ann. Chim. (Rome)* **53**, 848 (1963); *Gazz. Chim. Ital.* **91**, 1168 (1961); **95**, 1258 (1965); M. Basile and M. G. Vigorita, *Atti Soc. Peloritana Sci. Fis., Mat. Nat.* **15**, 199 (1969).

⁶⁹ O. Ceder, U. Stenhede, K.-I. Dahlquist, J. M. Waisvisz, and M. G. van der Hoeven, *Acta Chem. Scand.* **27**, 1914 (1973).

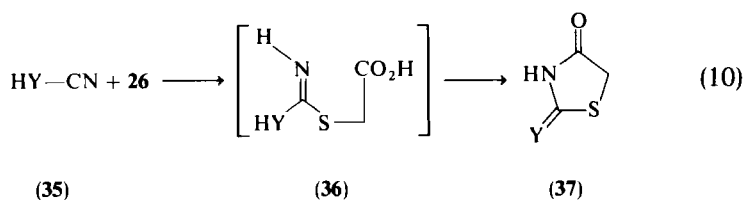
⁷⁰ O. Ceder and U. Stenhede, *Acta Chem. Scand.* **27**, 1923 (1973).

⁷¹ A. E. Kretov and A. S. Bepalyi, *Zh. Obshch. Khim.* **33**, 3323 (1963).

⁷² A. E. Kretov and A. S. Bepalyi, *Zh. Obshch. Khim.* **34**, 3365 (1964).

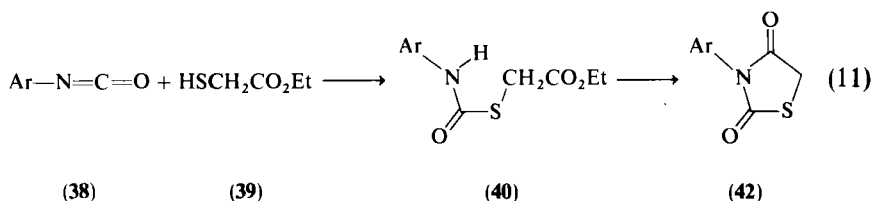
⁷³ G. Satzinger, *Justus Liebigs Ann. Chem.* **665**, 150 (1963).

⁷⁴ S. Kambe, K. Saito, H. Kishi, T. Hayashi, and A. Sakurai, *Synthesis* p. 839 (1977).

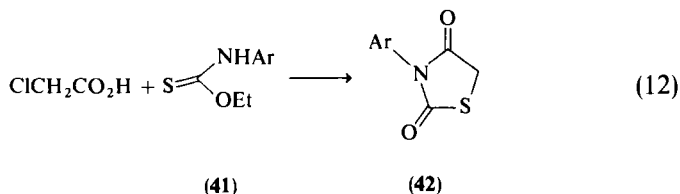


The isolation and *E,Z*-configurational assignments of 2-cyanomethylene-3-methyl-4-thiazolidinone have been reported,⁷⁰ thus correcting previous structural assignments.⁷³

N-Aryl-substituted diones (**2**) have been conveniently synthesized by reaction of an aryl isocyanate (**38**) with ethyl thioglycolate (**39**) in the presence of a basic catalyst, such as tri-*n*-propylamine or metallic sodium [Eq. (11)].⁷⁵ At temperatures less than 110°, the noncyclized intermediate **40** has been isolated.⁷⁵



Condensation of monochloroacetic acid with an arylthiourethan (**41**) in glacial acetic acid leads to **42** [Eq. (12)].⁷⁶ With alkylthiourethans, reaction temperatures must be maintained at 160°–170°.⁷⁷ Simultaneous reaction of the starting materials or **42** with aromatic aldehydes affords high yields of the 5-arylidene derivatives.⁷⁶ Similarly, arylamides of arylsulfonylcyanothioacetic acids condense with α -halocarboxy compounds to afford 2-substituted 4-thiazolidinones.⁷⁸



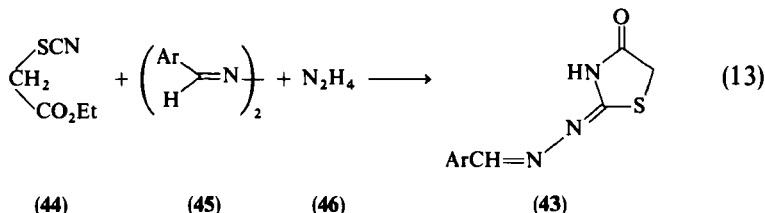
⁷⁵ M. Pergal, K. Popov-Pergal, and N. Kobilarov, *Synthesis* p. 190 (1976).

⁷⁶ E. V. Vladzimirskaya, *Zh. Obshch. Khim.* **32**, 1608 (1962).

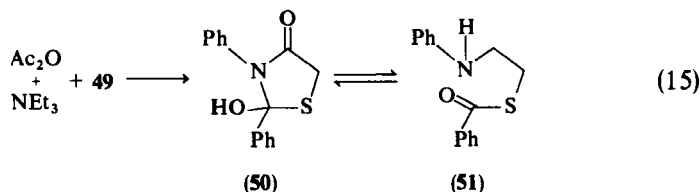
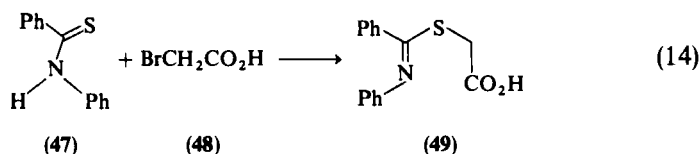
⁷⁷ E. V. Vladzimirskaya, *Zh. Obshch. Khim.* **32**, 2019 (1962).

⁷⁸ A. N. Borisevich, S. A. Shulezhko, and P. Pel'kis, *Khim. Geterotsikl. Soedin.* p. 368 (1966); V. M. Neplyuev, Yu. N. Usenko, R. Dubenko, and P. S. Pel'kis, *ibid.* p. 1194 (1970).

A convenient synthesis [Eq. (13)] of 2-arylidenehydrazono-4-thiazolidinone (**43**) from ethyl thiocynoacetate (**44**), arylideneazines (**45**), and hydrazine hydrate (**46**) has been reported.⁷⁹ Presumably, the reaction proceeds via the intermediary hydrazone, which condenses with **44** to give **43**. Subsequently, condensation of **43** with the aromatic aldehyde, generated *in situ* from disproportionation of the azine with hydrazine, affords the 5-arylidene derivative. The reaction of **44** with ammonium acetate and an aromatic aldehyde gives 5-arylidene-2-imino-4-thiazolidinones.⁸⁰



The reaction of thiobenzanilide (**47**) with bromoacetic acid (**48**) in the presence of triethylamine affords *S*-carboxymethylisothiobenzanilide (**49**) [Eq. (14)], which, when treated with acetic anhydride and triethylamine, gives the tentatively assigned pseudobase **50** [Eq. (15)].⁸¹ When **50** is subjected to either ethanol, benzene, or chloroform, benzoylthioglycolic acid anilide (**51**) is isolated; a mechanism has been proposed.⁸¹



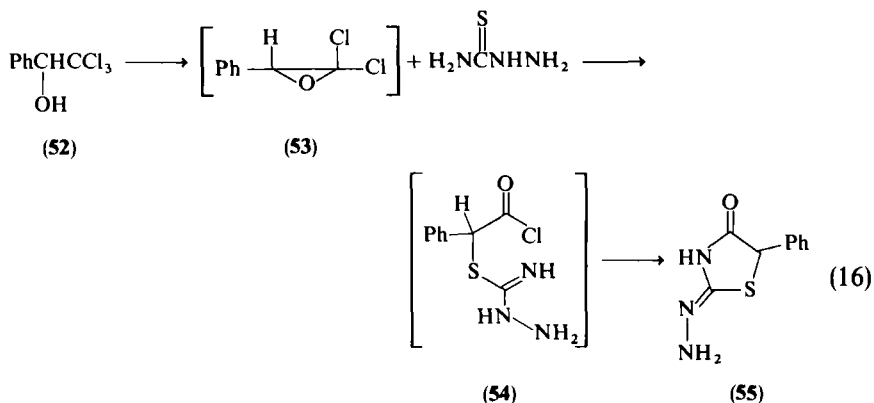
Phenyl(trichloromethyl)carbinol (**52**), when dissolved in ethylene glycol containing potassium hydroxide, is converted into an intermediate epoxide **53**, which reacts with thiosemicarbazide to generate the postulated **54**.⁸² Subsequent cyclization of **54** gives a 10% yield of **55** [Eq. (16)].⁸²

⁷⁹ S. Kambe and T. Hayashi, *Bull. Chem. Soc. Jpn.* **45**, 952 (1972).

⁸⁰ S. Kambe, T. Hayashi, H. Yasuda, and A. Sakurai, *Nippon Kagaku Zasshi* **92**, 867 (1971); S. Kambe and T. Hayashi, *Bull. Chem. Soc. Jpn.* **45**, 3192 (1972).

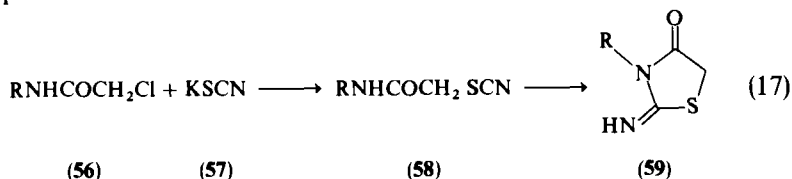
⁸¹ A. Shaikh, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jpn.* **43**, 453 (1970).

⁸² W. Reeve and E. R. Barron, *J. Org. Chem.* **40**, 1917 (1975).

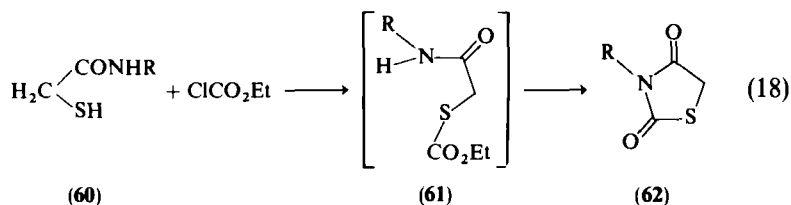


2. Formation of the 2,3-Bond

2-Haloacetamides (**56**) react with potassium thiocyanate (**57**) to give 2-thiocyanatoacetamides (**58**), which cyclize in proton-donor solvents to the 2-imino-4-thiazolidinones (**59**) [Eq. (17)].⁸³ Similarly, 5-nitro-2-furaldehyde chloroacetylhydrazone and **57** give 2-imino-3-(5-nitrofurfurylidene-amino)-4-thiazolidinone.⁸⁴ Bis-cyclizations have also been successfully accomplished.⁸⁵



Substituted thioglycolamides (**60**) are converted with ethyl chloroformate, via an intermediate carbonate **61**, to the corresponding thiazolidine-2,4-diones (**62**) upon distillation [Eq. (18)].⁸⁶



⁸³ E. Schröpl and R. Pohloudek-Fabini, *Pharmazie* **23**, 638 (1968); **24**, 96 (1969).

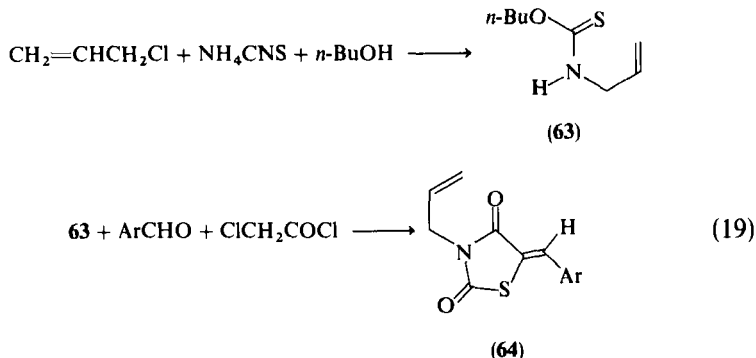
⁸⁴ F. F. Ebetino and G. Gever, *J. Org. Chem.* **27**, 188 (1962).

⁸⁵ Yu. V. Svetkin, Kh. F. Bikbaeva, E. M. Tsyrlina, and D. Ya. Mukhametova, *Zh. Obshch. Khim.* **46**, 2111 (1976).

⁸⁶ H. Kornowski and M. Trichot, *Bull. Soc. Chim. Fr.* p. 763 (1965).

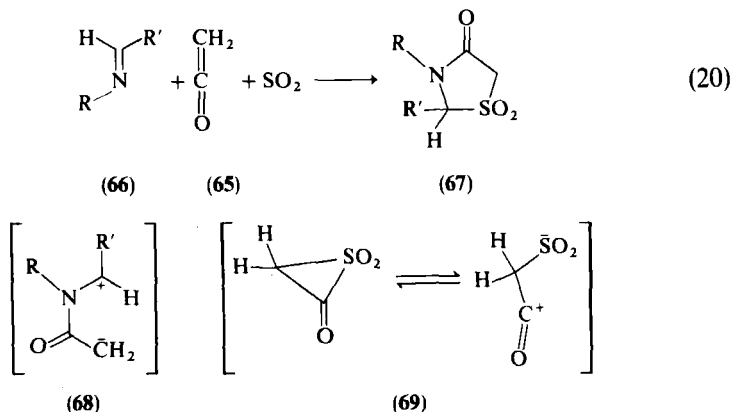
3. Formation of the 1,5-Bond

Allyl chloride was treated with ammonium thiocyanate in refluxing *n*-butanol to give thiourethan **63**, which when reacted with α -chloroacetyl chloride and benzaldehyde gave the 5-arylidene dione **64** [Eq. (19)].⁸⁷



4. Formation of the 1,2- and 3,4-Bonds: Cycloaddition Process

During the study of the reaction of ketene **65** with imines **66** in sulfur dioxide, substituted thiazolidin-4-one 1,1-dioxides (**67**) are formed [Eq. (20)], rather than the expected azetidinones.⁸⁰ This cycloaddition was initially suggested to proceed through a 1,4-dipolar species **68**⁸⁸; whereas later, a (3 + 2)-cycloaddition, via a 1,3-dipolar intermediate **69**, was demonstrated to support the results better.⁸⁵ This ketene-sulfur dioxide adduct **69** reacts



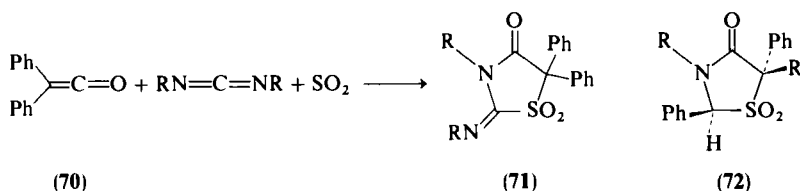
⁸⁷ L. I. Petlichna, M. M. Turkevich, and V. M. Vvedenskii, *Ukr. Khim. Zh.* **29**, 170 (1963).

⁸⁸ A. Gomes and M. M. Joullié, *Chem. Commun.* p. 935 (1967).

cleanly with aromatic amines⁸⁸ and imines,⁸⁹ as well as with carbon–nitrogen double bonds.^{90,91}

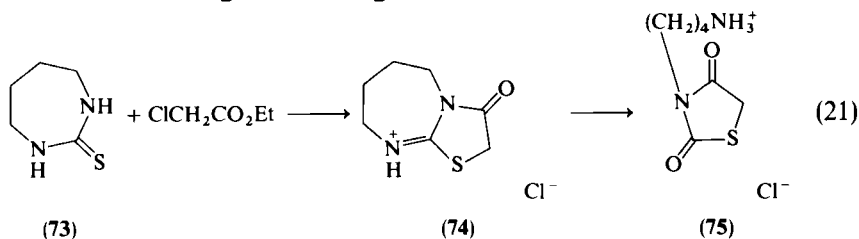
5. Formation of the 1,2- and 1,5-Bonds: Cycloaddition Process

Diphenylketene (**70**) undergoes reaction with diisopropylcarbodiimide in liquid sulfur dioxide to give a near quantitative yield of **71**; the results suggest a two-step process via a 1,4-dipolar intermediate similar to **68**.⁹² Phenylalkylketenes similarly react with Schiff bases in liquid sulfur dioxide, giving only the *trans*-thiazolidinone 1,1-dioxides (**72**).⁹³



B. RING INTERCONVERSIONS

Tetrahydro-1*H*-1,3-diazepine-2-thiol (**73**), when heated with ethyl chloroacetate, gives **74** while the reaction of **73** with chloroacetic acid in aqueous medium affords 3-(δ -aminobutyl)thiazolidine-2,4-dione (**75**) [Eq. (21)], via initial generation **74**, followed by hydrolysis.⁹⁴ Substituted 2-mercaptoimidazolines undergo similar ring transformations.^{95–97}



⁸⁹ A. S. Gomes and M. M. Joullié, *J. Heterocycl. Chem.* **6**, 729 (1969).

⁹⁰ J. M. Bohan and M. M. Joullié, *J. Org. Chem.* **38**, 2652 (1973).

⁹¹ Z. Lysenko and M. M. Joullié, *J. Org. Chem.* **41**, 3925 (1976).

⁹² W. T. Brady and E. D. Dorsey, *J. Org. Chem.* **35**, 2732 (1970).

⁹³ J. M. Decazes, J. L. Luche, H. B. Kagan, R. Parthasarathy, and J. Ohrt, *Tetrahedron Lett.* p. 3633 (1972).

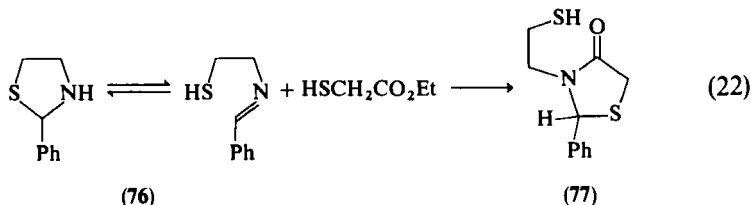
⁹⁴ V. K. Chadha, H. S. Chaudhary, and H. K. Pujari, *Austr. J. Chem.* **22**, 2697 (1969).

⁹⁵ V. K. Chadha, H. S. Chaudhary, and H. K. Pujari, *Indian J. Chem.* **8**, 885 (1970); H. S. Chaudhary and H. K. Pujari, *ibid.* **10**, 766 (1972).

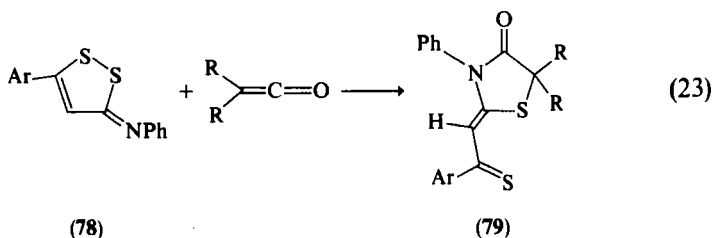
⁹⁶ J. Sawlewicz, K. Wisterowicz, and H. Ciurach, *Acta Pol. Pharm.* **33**, 681 (1976).

⁹⁷ I. I. Chizhevskaya and M. I. Zavadsкая, *Zh. Org. Khim.* **4**, 1116 (1968).

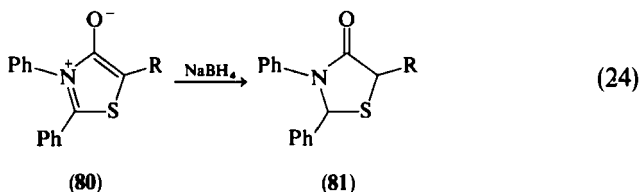
Thiazolidines (**76**) undergo facile ring-chain tautomerism, thus affording a latent source of thiol-imine, which can be trapped with ethyl mercaptoacetate at 100°–110° to afford **77** in low yield [Eq. (22)].⁶³ If the corresponding acid is used and water is continuously removed, the yield of **77** approaches 75%.



5-Aryl-3-*N*-phenylimino-1,2-dithiol (**78**) condenses with a ketene to give **79** [Eq. (23)] which, when warmed, reverts to **78**.⁹⁸ Substituted ketenes with **78** give the corresponding 5-substituted **79**. The related 5-phenylamino-3-imino-1,2,4-dithiazoline, when heated in acetic anhydride, rearranges to afford 2-acetylimino-3-phenyl-4-thiazolidinone (95%).⁹⁹



Reduction of mesoionic 2,3-diphenyl-4-thiazolinones (**80**; R = H) with lithium aluminum hydride gives only resinous material, and only unreacted starting material with sodium borohydride. However, thiazolinones with 5-phenyl or acyl substituents (**80**; R = Ph or R'CO) are readily reduced with sodium borohydride to the thiazolidin-4-ones **81** (R = Ph or R'CHOH) [Eq. (24)].¹⁰⁰



⁹⁸ G. Hervieu, P. Rioult, and J. Vialle, *Bull. Soc. Chim. Fr.* p. 4380 (1971).

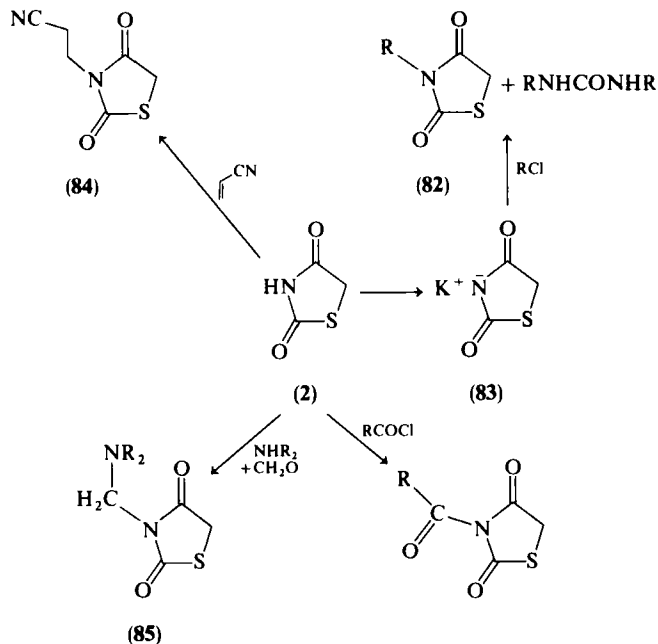
⁹⁹ H. Behringer and D. Weber, *Chem. Ber.* **97**, 2567 (1964).

¹⁰⁰ Z. Takayanagi, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.* **40**, 2930 (1967).

III. Reactions of 4-Thiazolidinones

A. 3-SUBSTITUTION

2,4-Thiazolidinedione (**2**) is readily alkylated at the 3-position when treated with alkyl chlorides for 5 minutes at 142°–145° in DMF with potassium carbonate (Scheme 2).¹⁰¹ Prolonged reaction at temperatures above 120° resulted in decreased yields of **82** and in formation of 1,3-dialkylated ureas via ring degradation.¹⁰¹ Treatment of the potassium salt of **2** (**83**) with primary alkyl halides¹⁰² has been demonstrated to be the most versatile alkylation procedure, by which a wide range of functionalized side chains have been appended to the 3-position.^{103–106} 3-Methylthiazolidinedione (**82**; R = Me) is conveniently prepared from **2** by treatment with



SCHEME 2

¹⁰¹ G. Irick, *J. Heterocycl. Chem.* **8**, 847 (1971).

¹⁰² C.-P. Lo and E. Y. Shropshire, *J. Am. Chem. Soc.* **75**, 4853 (1953).

¹⁰³ S. K. Mallick, A. R. Martin, and R. G. Lingard, *J. Med. Chem.* **14**, 528 (1971).

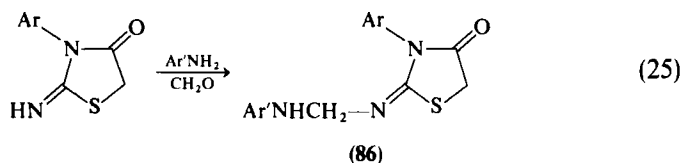
¹⁰⁴ N. N. Turkevich and S. M. Bartylyak, *Farm. Zh. (Kiev)* **28**, 18 (1973).

¹⁰⁵ V. A. Zdorenko and E. V. Vladzimirskaya, *Farm. Zh. (Kiev)* **32**, 28 (1977); I. I. Soronovich and E. V. Vladzimirskaya, *ibid.* **30**, 13 (1975); E. V. Vladzimirskaya and B. M. Kirichenko, *ibid.* pp. 32 and 41.

¹⁰⁶ N. Turkevich and S. A. Yurzhenko, *Khim. Geterotsikl. Soedin., Sb.* **3**, 129 (1971).

diazomethane¹⁰³ or dimethyl sulfate and potassium hydroxide.¹⁰⁶ The potassium salt **83** is similarly acylated by treatment with an acyl halide in acetone.¹⁰⁶

3-Pyridylethyl derivatives of **2** are formed by reaction of α - or γ -vinylpyridine with **2**.¹⁰⁷ Treatment of **1** or **2**, as well as the 5-arylidene derivatives, with acrylonitrile in the presence of pyridine results in formation of **84** by cyanoethylation on the ring nitrogen (Scheme 2); however, cyanoethylation of 5-aryl-2-iminothiazolidinones involves the exocyclic nitrogen.¹⁰⁸ Aminoalkylation (Mannich reaction) of **2** or 2-aryl-4-thiazolidinones with formaldehyde and amines in warm alcoholic solvents affords the desired 3-alkylated product **85** (Scheme 2),^{109,110} whereas 3-aryl-2-iminothiazolidinones react with substituted anilines and aliphatic amines and formaldehyde to give the 2-arylaminomethyl derivatives **86** [Eq. (25)].¹¹¹



N-Alkylation of **3** favors 3-substitution.¹¹²

1,3-Thiazolidin-2-one has been synthesized by cyclization of 2-iodoalkyl isothiocyanates.¹¹³

B. 4-SUBSTITUTION

Conversion of the 4-C=O group of **62** into a thione function creates an isomer of rhodanine (**5**) called isorhodanine (**87**; R = H), which displays enhanced chemical reactivity. Treatment of **62** with phosphorus pentasulfide in dioxane affords **87**.¹¹⁴⁻¹¹⁷ Isorhodanines (**87**) react with

¹⁰⁷ M. A. Lazovskaya, S. N. Baranov, A. K. Sheinkman, and A. A. Rok, *Khim. Geterotsikl. Soedin.* p. 599 (1971).

¹⁰⁸ A. H. Harhash, M. E. E.-D. Sobhy, M. H. Elnagdi, and K. M. Foda, *Egypt. J. Chem.* **15**, 11 (1972).

¹⁰⁹ V. E. Kononenko, B. E. Zhitar, and S. N. Baranov, *Zh. Org. Khim.* **9**, 61 (1973).

¹¹⁰ P. N. Bhargava and S. C. Sharma, *Bull. Chem. Soc. Jpn.* **38**, 909 (1965).

¹¹¹ Yu. V. Svetkin, S. A. Vasil'eva, and V. M. Pronina, *Khim. Geterotsikl. Soedin.* p. 365 (1974); *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **18**, 1061 (1975); *Chem. Abstr.* **83**, 178908 (1975).

¹¹² V. G. Zubenko, *Farm. Zh. (Kiev)* **26**, 11 (1971).

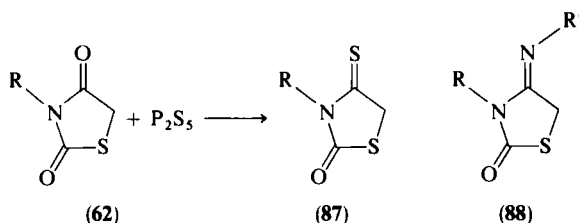
¹¹³ P. D. Woodgate, H. H. Lee, P. S. Rutledge, and R. C. Cambie, *Synthesis* p. 322 (1977).

¹¹⁴ A. P. Grishchuk, I. D. Komaritsa, and S. N. Baranov, *Khim. Geterotsikl. Soedin.* p. 706 (1966); p. 664 (1967).

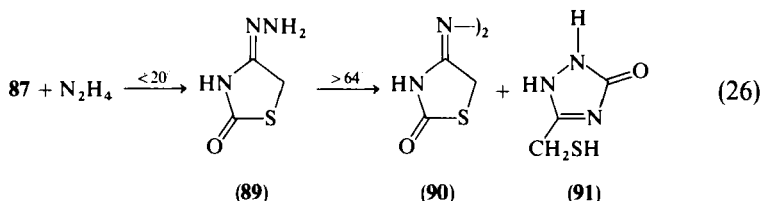
¹¹⁵ N. E. Plevachuk, *Farm. Zh. (Kiev)* **25**, 28 (1970).

¹¹⁶ J. S. Davidson, *Chem. Ind. (London)* p. 618 (1974).

¹¹⁷ R. O. Kochkanyan, *Khim. Geterotsikl. Soedin., Sb.* **3**, 140 (1971).



hydroxylamine to liberate hydrogen sulfide, even in the cold, to give the 4-oxime (**88**; $\text{R}' = \text{OH}$).¹¹⁸ Amines^{114,117-121} and substituted hydrazines^{115-119,122,123} readily condense with **87** below 100° . Alcoholic hydrazine reacts with **87** at 20° to afford the corresponding hydrazone **89**, which when warmed to ca. 64° causes disproportionation to occur, giving the azine **90** and a rearranged thiazolone **91** [Eq. (26)].¹²² Hydrolysis of the 4-imino groups regenerates the starting 4-one. Direct conversion of **62** to **88** has been demonstrated by its treatment with phosphorus oxychloride and subsequent addition of an amine in alcohol.¹²⁴



C. 5-SUBSTITUTION

1. Condensation Reactions

4-Thiazolidinones are condensed with aromatic aldehydes, usually by refluxing in glacial acetic acid with fused sodium acetate for lengths of time dependent upon ring substituents¹²⁵; e.g., **92** with benzaldehyde yields 73% of **93** after 2 hours of refluxing [Eq. (27)].¹²⁶ This general procedure has been

¹¹⁸ I. D. Komaritsa and A. P. Grishchuk, *Khim. Geterotsikl. Soedin.* p. 706 (1968).

¹¹⁹ O. L. Grom, *Farm. Zh. (Kiev)* **26**, 77 (1971).

¹²⁰ I. D. Komaritsa and N. E. Plevachuk, *Khim. Geterotsikl. Soedin.*, **3**, 150 (1971).

¹²¹ N. A. L. Kassab, M. H. E. Nagdy, and H. A. R. Ead, *J. Prakt. Chem.* **315**, 265 (1973).

¹²² O. P. Shvaika, S. N. Baranov, and V. N. Artemov, *Dokl. Akad. Nauk SSSR* **186**, 1102 (1969); *Khim. Geterotsikl. Soedin.* p. 39 (1971); *Zh. Org. Khim.* **6**, 2353 (1970).

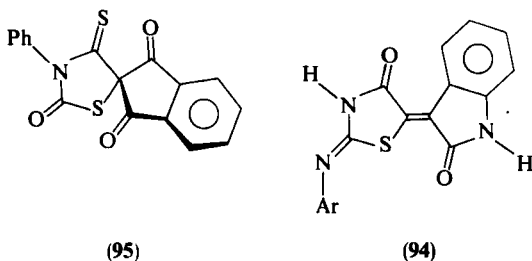
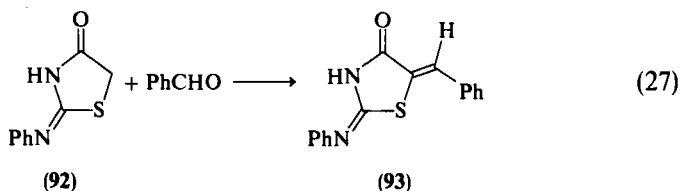
¹²³ P. G. Sekachev, *Khim. Geterotsikl. Soedin.* p. 1351 (1973).

¹²⁴ E. Enders and W. Stendel, German Patent 2,226,242 (1973); *Chem. Abstr.* **80**, 82946 (1974); R. O. Kochkanyan, S. N. Baranov, I. P. Borodai, and A. N. Zaritovskii, USSR Patent 474,535 (1975); *Chem. Abstr.* **83**, 114386 (1975).

¹²⁵ E. Koltai, J. Nyitrai, and K. Lempert, *Tetrahedron* **29**, 2781 (1973).

¹²⁶ A. Mustafa, W. Asker, A. F. A. M. Shalaby, A. H. Harhash, and R. Daguer, *Tetrahedron* **20**, 25 (1964).

used to condense 2-iminothiazolidinones (**3**),^{12,15,17,19-24,40,53,126-129} diones (**2**),^{77,94-96,103-106,119,129,130,131} 4-imino-2-ones (**88**),^{120,121} 2-one-4-thiones (**87**),^{114,117} and substituted **1**⁶⁵ with aromatic aldehydes. Condensation of 2-arylimino derivatives (**92**) with aldehydes in ethanol, with traces of piperidine, gives very low yields of the corresponding 5-benzylidene derivative **93**, whereas the 2-benzylimino derivative does not react with aromatic aldehydes under these conditions.¹³² 3-Substituted 2-arylimino **10** ($R = H$) affords good yields of the benzylidene derivatives utilizing piperidine as catalyst.¹³² The attempted aldol condensation of 2,3-diphenyl-4-thiazolidinone with benzaldehyde with either sodium acetate-acetic acid, ammonia (ammonium chloride) in aqueous ethanol, or piperidine in benzene was unsuccessful; however, the use of sodium ethoxide in anhydrous benzene afforded the corresponding 5-benzylidene derivative.¹³³ Some major studies prior to 1960 reported the condensation of the 5-methylene moiety with aromatic aldehydes, as well as with simple aliphatic and cyclic ketones.^{1,134} Condensation of **2** with benzaldehyde has also been reported from the hydrolysis of **24** ($R = Ar$, $R' = H$) and loss of hydrazine.¹³⁵



¹²⁷ E. B. Akerblom, *J. Med. Chem.* **17**, 609 (1974).

¹²⁸ V. G. Zulenکو and M. M. Turkevich, *Farm. Zh. (Kiev)* **20**, 6 (1965).

¹²⁹ S. N. Baranov, *Zh. Obshch. Khim.* **32**, 1230 (1962).

¹³⁰ W. H. Burton, W. L. Budde, and C. C. Cheng, *J. Med. Chem.* **13**, 1009 (1970).

¹³¹ L. Musial and J. Staniec, *Rocz. Chem.* **39**, 839 (1965); **38**, 1105 (1964).

¹³² I. I. Chizhevskaya, R. S. Kharchenko, and N. N. Khovratovich, *Khim. Geterotsikl. Soedin.* **3**, 642 (1967).

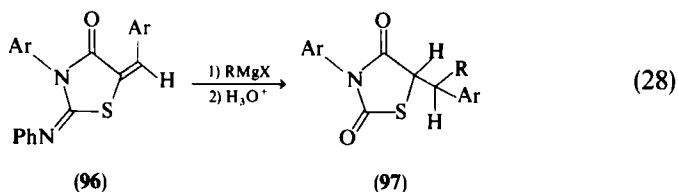
¹³³ F. C. Brown, R. S. Jones, and M. Kent, *Can. J. Chem.* **41**, 817 (1963).

¹³⁴ A. Mustafa, W. Asker, and M. E. E.-D. Sobhy, *J. Am. Chem. Soc.* **82**, 2597 (1960).

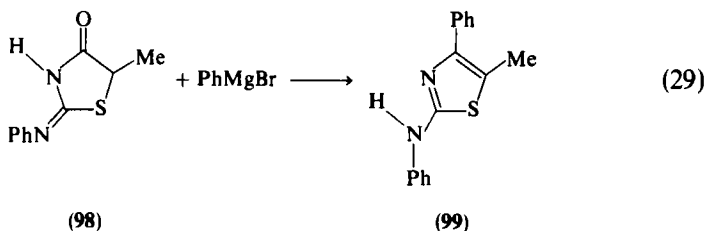
¹³⁵ Yu. V. Svetkin and A. N. Minlibaeva, *Zh. Org. Khim.* **7**, 1301 (1971).

Activated ketones, for example isatin¹³⁶ or acenaphthenequinone,¹³⁷ have been similarly condensed with **92** at ca. 150° for several hours with acetic acid and sodium acetate forming, for example, **94**, **3**, or **42**. Fusing **87** (R = Ph) with excess phthalic anhydride in the presence of an alkaline catalyst gives (84%) spiro[2-oxo-3-phenyl-4-thioxo-1,3-thiazolidine-5,2'-indane-1',3'-dione] (**95**).¹¹⁷

The 5-arylidene derivatives (e.g., **96**) react with Grignard reagents via 1,4-conjugate addition to the exocyclic double bond to afford **97** [Eq. (28)]; heterocyclic ring opening does not occur under these conditions.^{121,126,134,138} Other nucleophiles, such as *p*-thiocresol and piperidine, add 1,4 to exocyclic double bonds to give the simple adducts **97** (R = SAr and NR'₂, respectively).¹³⁴ 5-Methyl-3-phenyl-2-phenylimino-4-thiazolidinone undergoes



facile heteroring opening upon treatment with Grignard reagents,¹²⁶ but with **98**, 1,2-addition occurs with phenylmagnesium bromide treatment, followed by dehydration to afford **99** [Eq. (29)].¹²⁶



Catalytic reduction of the 5-exocyclic bond cannot easily be accomplished due to the presence of the sulfur; however, sodium amalgam reduces the bond in good yields.¹²⁸ Bromination of the exocyclic bond is reported.^{20,22,24}

¹³⁶ R. P. Rao, *J. Sci. Ind. Res. Sect. B* **19**, 29 (1960); R. P. Rao and S. R. Singh, *J. Indian Chem. Soc.* **50**, 752 (1973); R. P. Rao and S. Raj, *ibid.* p. 366.

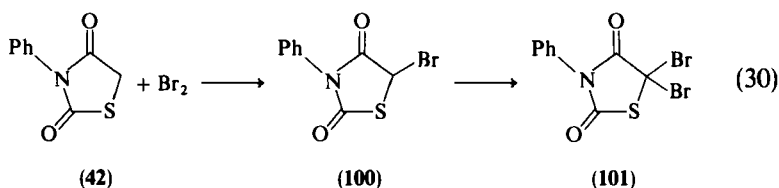
¹³⁷ A. P. Karishin and Yu. V. Samusenko, *Zh. Org. Khim.* **1**, 1003 (1965); A. P. Karishin, A. I. Timchenko, G. F. Dzhurka, Yu. V. Samusenko, T. F. Baklan, and G. M. Lysenko, *Khim. Geterotsikl. Soedin.* p. 704 (1965).

¹³⁸ A. Mustafa, W. Asker, S. Khattab, M. E. E.-D. Sobhy, A. M. Fleifel, and K. A.-Elazayem, *J. Am. Chem. Soc.* **82**, 2029 (1960).

Treatment of 2,3-diphenyl-5-benzylidene-4-thiazolidinone with aluminum chloride (3.5 mol) in benzene results (perhaps unexpectedly) in the formation (70%) of 2,3,5-triphenyl-5-benzyl-4-thiazolidinone, by 1,2-addition to the exocyclic bond.¹³⁹

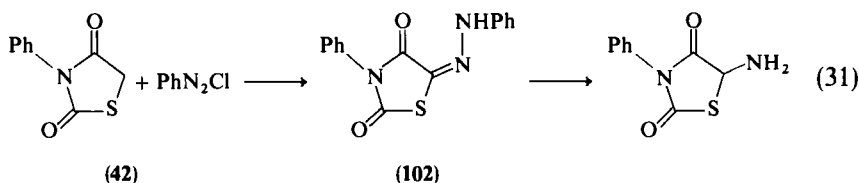
2. Halogenation

When 3-phenyl-2,4-thiazolidinone (**42**) is brominated in acetic acid, it gives the 5-bromo derivative (**100**), which upon further bromination forms (85–90%) the 5,5-dibromo derivative (**101**) [Eq. (30)].¹⁴⁰ Facile nucleophilic displacement of the halide atom on **100** by arylamines has been demonstrated.¹⁴¹



3. Coupling Reactions

An amino group has been introduced at the 5-position of the thiazolidine-dione nucleus by coupling of the reactive methylene group with benzenediazonium chloride at 0°–5°, followed by reduction of **102** with sodium hydrosulfite [Eq. (31)].¹⁴² The tautomeric structural assignment of **102** has



¹³⁹ R. H. Snider, L. M. Beale, R. Gaillard, P. Coggon, A. T. McPhail, and F. C. Brown, *Int. J. Sulfur Chem., Part A* **1**, 191 (1971).

¹⁴⁰ N. C. Misra and K. K. Patnaik, *J. Inst. Chem., Calcutta* **44**, 12 (1972).

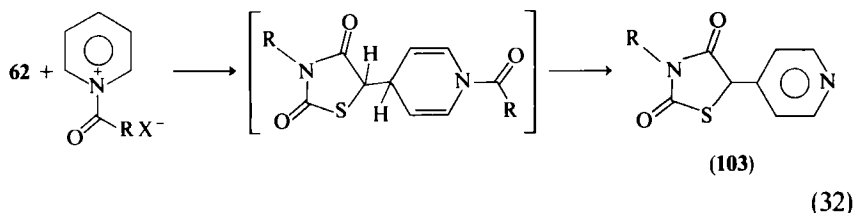
¹⁴¹ S. N. Baranov and R. O. Kochkanyan, *Khim. Farm. Zh.* **4**, 25 (1970).

¹⁴² P. N. Bhargava and S. C. Sharma, *Bull. Chem. Soc. Jpn.* **35**, 1926 (1962); P. N. Bhargava and P. R. Singh, *J. Sci. Ind. Res., Sect. C* **20**, 209 (1961); P. N. Bhargava and M. R. Chaurasia, *J. Pharm. Sci.* **58**, 896 (1969).

been questioned;¹⁴³ however, the hydrazone form almost certainly predominates. Isorhodanines (**87**)^{114,144} as well as imino compounds **10** ($R = H$)^{27,36,38,145,146} undergo facile coupling with aryldiazonium salts at the 5-position. Heteroaryldiazonium salts have also been successfully used.^{10,11,140} The use of diazotized sulfanilamide^{20,147} or arsanilic¹⁴⁷ acid, which decompose with loss of nitrogen, gives attachment of 4-sulfonamido- or arsono-phenyl moieties at the 5-position of 2-imino-4-thiazolidinones.

4. Heteroarylation

The heteroarylation of thiazolidinones has been accomplished with *N*-acyl-pyridinium, -quinolinium, -isoquinolinium, and -acridinium salts [Eq. (32)].¹⁴⁸ Alkaline hydrolysis of **103** serves as a convenient source of heterocyclic thioglycolic acids.



D. 1-SUBSTITUTION: OXIDATION

Oxidation of 3-substituted 4-thiazolidinones (e.g., **104**) with permanganate in acetic acid produces the corresponding sulfone **106** [Eq. (33)]^{29,36,58,89,146,147,149-151} via the sulfoxide intermediate (**105**). Dione **2**

¹⁴³ P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Indian Chem. Soc.* **48**, 719 (1971).

¹⁴⁴ A. P. Grishchuk and I. D. Komaritsa, *Khim. Khim. Tekhnol.* p. 22 (1969).

¹⁴⁵ R. P. Rao and S. R. Singh, *J. Indian Chem. Soc.* **50**, 600 (1973); R. P. Rao, *ibid.* **38**, 784 (1961); *Proc. Natl. Acad. Sci. India, Sect. A* **30**, 179 (1961).

¹⁴⁶ P. N. Bhargava and M. R. Chaurasia, *J. Chem. U.A.R.* **12**, 149 (1969).

¹⁴⁷ B. C. Mahanta, A. K. Panigrahi, and M. K. Rout, *J. Indian Chem. Soc.* **47**, 707 (1970).

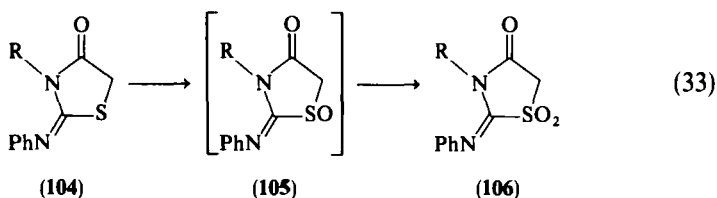
¹⁴⁸ A. A. Deikalo, A. K. Sheinkman, and S. N. Baranov, *Khim. Geterotsikl. Soedin.* pp. 1105 and 1359 (1972); **6**, 130 (1970).

¹⁴⁹ I. I. Chizhevskaya, A. Z. Malinnikova, and N. N. Khovratovich, *Khim. Geterotsikl. Soedin.* p. 96 (1971).

¹⁵⁰ I. I. Chizhevskaya, A. Z. Milinnikova, and N. M. Pliss, *Vesti Akad. Nauk B. SSR, Ser. Khim. Nauk* p. 97 (1969); *Chem. Abstr.* **73**, 3834 (1970).

¹⁵¹ A. R. Surrey, U.S. Patent 3,377,355 (1968); *Chem. Abstr.* **69**, 59227 (1968).

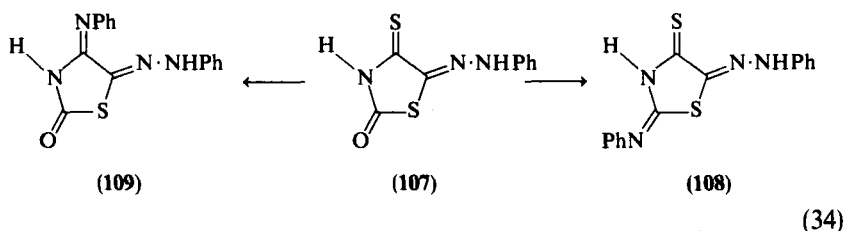
is inert to 5-oxidation by permanganate even at elevated temperatures.¹⁵⁰ With peracetic acid,¹⁵¹ 3-substituted 4-thiazolidinones generate either the sulfoxide^{68,151} or, with acetic anhydride¹⁵² or more severe conditions,¹⁵¹ the corresponding sulfone.



E. 2-SUBSTITUTION

1. Condensation

5-Phenylazo-2-thiazolidinone-4-thione (**107**), when treated with aniline and sodium acetate in acetic acid under reflux for 20 minutes, is converted into **108** in 54% yield [Eq. (34)], whereas, with aniline in methanol at 60° for 1.5 hours, it is transformed by 4-substitution to **109**.¹⁴⁴ (Hydrazone tautomers, as shown, are likely for **107**–**109**.)



2. Hydrolysis of Imino Groups

Iminothiazolidinones (e.g., **10**) easily undergo acid–base hydrolysis under mild conditions to afford the corresponding diones (**42**).^{6,7,10,26,28,30,40,43,72,80,85,94,99,128,135,146,153–155} The thiazolidine ring is cleaved at the

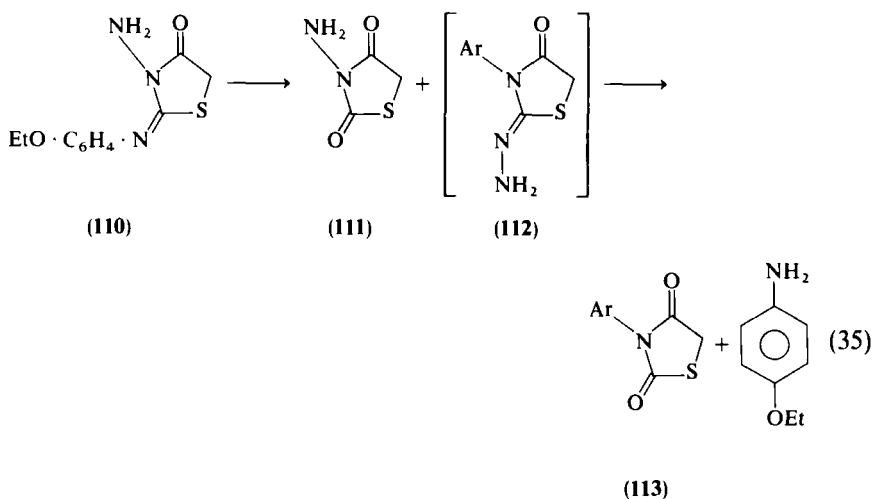
¹⁵² M. Susse and H. Dehne, *Z. Chem.* **15**, 303 (1975).

¹⁵³ Yu. V. Svetkin, L. B. Reznik, F. A. Amirkhanova, G. B. Bogolyuk, and F. N. Zainullina, *Zh. Obshch. Khim.* **34**, 977 (1968).

¹⁵⁴ A. Rahman, H. S. E. Gatica, and A. A. Khan, *Chem. Ind. (London)* p. 1422 (1962).

¹⁵⁵ Yu. V. Svetkin, S. A. Vasil'eva, and L. D. Tokareva, *Khim. Geterotsikl. Soedin.* p. 903 (1976).

N_3-C_4 bond on prolonged heating with hydrochloric acid in ethanol or acetic acid with formation of an N-substituted pseudohydantoic acids. In general, ascertaining the structure of 4-thiazolidinones by hydrolysis procedures can lead to erroneous conclusions, unless care is taken. For example, in establishing the amino group location, **110** was refluxed in concentrated hydrochloric acid for 30 minutes to give **111**, **113**, and *p*-ethoxyaniline; thus, hydrolysis of **110** proceeded with ring opening, and probably involved intermediate **112** [Eq. (35)].¹⁵⁶ Such acid-catalyzed tautomerisms are well documented for these compounds.¹⁵³ In basic solution, cleavage of the



thiazolidinone ring occurs with formation of **39**, which subsequently undergoes alkaline degradation to the substituted urea and mercaptoacetic acids in virtually quantitative yields.^{6,16,157,158}

3. Desulfurization of 2-Thione Derivatives

When rhodanine (**5**) and its 5-benzylidene derivatives not substituted in the 3-position are reacted with methyl iodide and an equal molar quantity of triethylamine in chloroform, the corresponding dione (**2**) is isolated in high yield.¹⁵⁹ Simple desulfurization of **5** with Raney nickel in aqueous

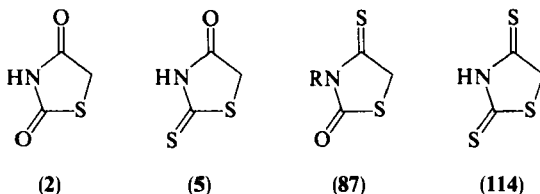
¹⁵⁶ L. I. Petlichna, *Farm. Zh. (Kiev)* **23**, 3 (1968).

¹⁵⁷ G. S. Skinner and R. M. Macnair, *J. Org. Chem.* **25**, 1164 (1960); G. S. Skinner and J. S. Elmslie, *ibid.* **24**, 1702 (1959).

¹⁵⁸ A. V. Shelud'ko, *Farm. Zh. (Kiev)* **16**, 21 (1961).

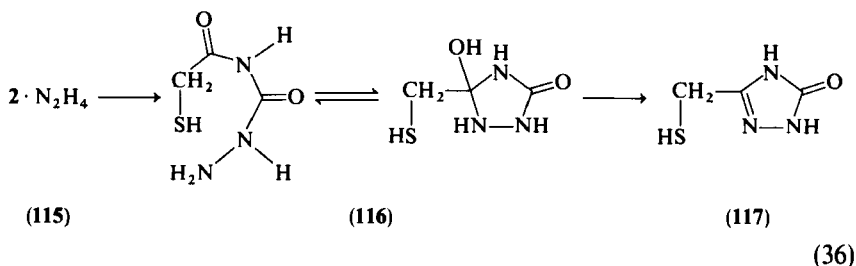
¹⁵⁹ A. I. Ginak, K. A. V'yunov, and E. G. Sochilin, *Zh. Prikl. Khim.* **45**, 460 (1972).

solution affords the α -mercaptoacetic acid from which mercapto group is eliminated and replaced by hydrogen.¹⁶⁰ Partial desulfurization by conversion of the 2-thiono group into a methylene group is accomplished either (a) with Raney nickel at ordinary temperatures at 30 atm H_2 in ethanol¹⁶¹ or (b) electrochemically,¹⁶² to give **1** in respectable yields. Isorhodanine (**87**; R = H) is prepared by boiling **2** with phosphorus pentasulfide in dioxane for 3 hours; neither rhodanine **5** nor thiorhodanine (**114**) were isolated.¹¹⁴



F. RING-OPENING REACTIONS

Under drastic acidic hydrolysis¹⁵⁶ or treatment with hydroxide or alkoxide,¹⁵⁸ 4-thiazolidinones are cleaved at the N_3-C_4 bond. The reaction of **2** with hydrazine at below 0° affords an adduct (**115**) which gives a positive test with Fehling's solution and, upon acidification, regenerates the starting dione **2**. At room temperature; however, **115** rearranges to **116** via cleavage of the N_1-C_2 bond,^{163,164} and subsequent cyclization to **117** occurs on heating in anhydrous solvents with traces of acid [Eq. (36)].^{163,165} In aqueous medium at room temperature, **116** is hydrolyzed to α -mercaptoacetic acid and semicarbazide.¹⁶³



¹⁶⁰ C. K. Bradsher, F. C. Brown, and R. J. Grantham, *J. Am. Chem. Soc.* **73**, 5377 (1951); G. G. Allen, D. McLean, and G. T. Newbold, *J. Chem. Soc.* p. 5053 (1952).

¹⁶¹ M. Stefanovic, A. Stojiljkovic, and A. Jokic, *Tetrahedron* **21**, 831 (1965).

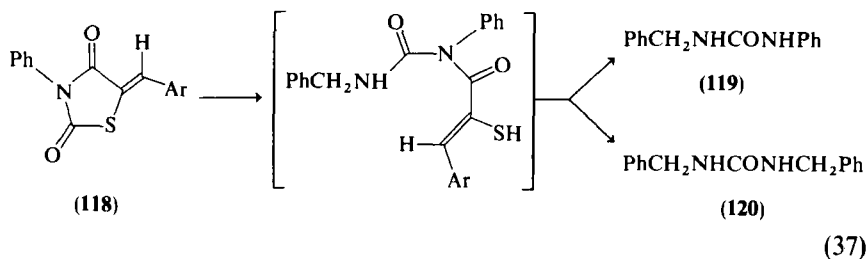
¹⁶² M. L. Girard and C. Draux, *Bull. Soc. Chim. Fr.* p. 3469 (1968).

¹⁶³ O. P. Shvaika, V. N. Artemov, and S. N. Baranov, *Khim. Geterotsikl. Soedin.* **6**, 991 (1970).

¹⁶⁴ E. B. Akerblom, *J. Med. Chem.* **17**, 609 (1974).

¹⁶⁵ V. N. Artemov, S. N. Baranov, N. A. Kovach, and O. P. Shvaika, *Dokl. Akad. Nauk SSSR* **211**, 1369 (1973).

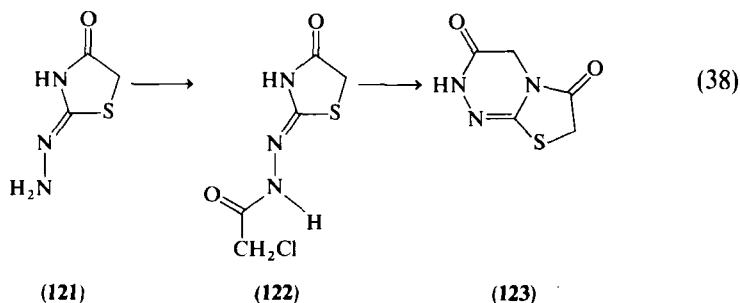
5-Arylidene-3-phenyl-2,4-thiazolidinones (**118**) undergo ring cleavage (N_1-C_2 and C_4-C_5 bonds) with excess benzylamine to give equimolar amounts of **119** and **120** [Eq. (37)].^{166,167}



G. RING-FORMATION REACTIONS

1. Cyclization between the 2,3-Positions

Treatment of thiosemicarbazide hydrochloride with acetic monochloroacetic anhydride affords **121**.¹⁶⁸ Further reaction with the anhydride gives **122**, which readily cyclizes to the 6,5-fused ring system **123** [Eq. (38)].¹⁵⁵



2-Phenylhydrazono-4-thiazolidinones (**124**) and their 5-substituted derivatives are cyclized upon treatment with formaldehyde or aromatic aldehydes to give the bicyclic structure **125**.¹⁶⁹ 5-Arylidene derivatives of **126** have been cyclized to **127** by initial treatment with chloroacetic acid, followed by hot acetic anhydride or concentrated sulfuric acid.¹⁷⁰

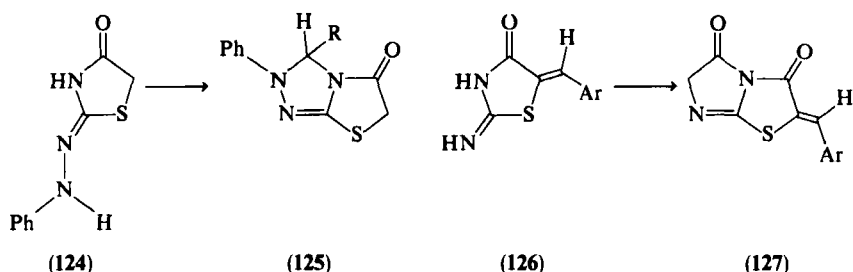
¹⁶⁶ A. R. A. Raouf, M. T. Omar, and M. M. Habashy, *J. Prakt. Chem.* **315**, 492 (1973).

¹⁶⁷ A. R. A. Raouf, M. T. Omar, and M. M. E. Attal, *Acta Chim. Acad. Sci. Hung.* **83**, 367 (1974).

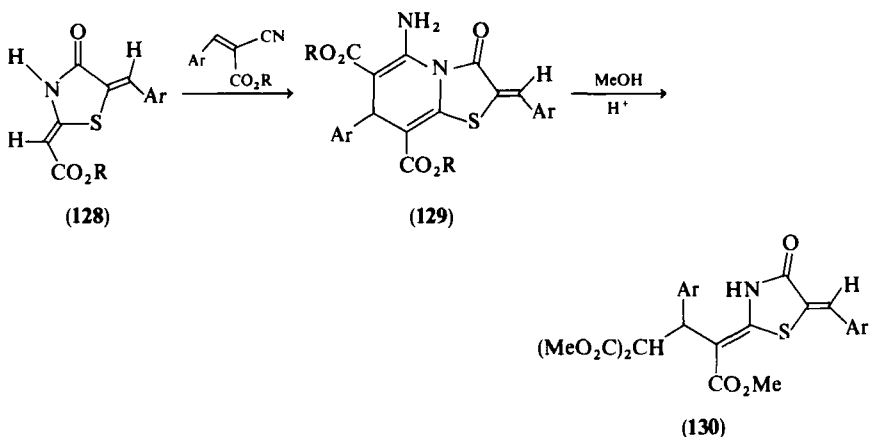
¹⁶⁸ Yu. V. Svetkin, A. N. Minlibaeva, and A. G. Mansurova, *Zh. Org. Khim.* **8**, 1722 (1972).

¹⁶⁹ N. A. E. Kassab, S. O. A. Alla, and H. A. R. Ead, *Z. Naturforsch., Teil B* **31**, 380 (1976).

¹⁷⁰ A. H. Harhash, M. H. Elnagdi, M. E. E.-D. Sobhy, and K. M. Foda, *Indian J. Chem.* **13**, 238 (1975).

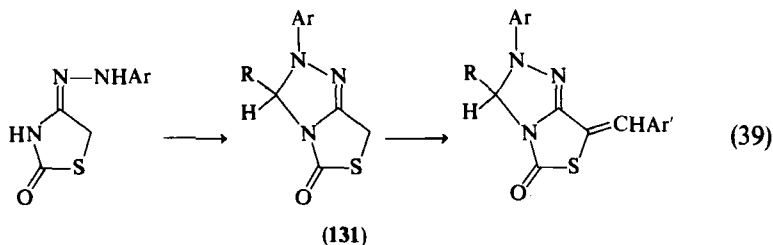


Reaction of α -cyanocinnamates with **128** gives the 7*H*-thiazolo[3,2-*a*]-pyridine derivative **129**, which upon hydrolysis in methanolic hydrochloric acid suffers cleavage of the pyridine ring to give **130**.⁷⁴



2. Cyclization between the 3,4-Positions

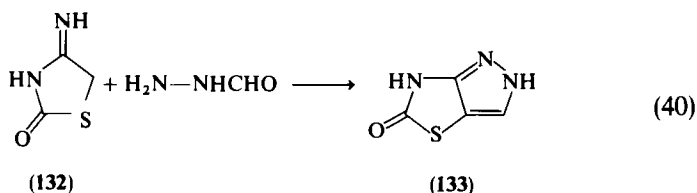
Cyclization of the 4-phenylhydrazono derivatives of 2-thiazolidinone with formaldehyde or aromatic aldehydes gives 2-phenyl-2,3-dihydrothiazolo[4,3-*c*]1,2,4-triazol-5-ones (**131**) [Eq. (39)]; subsequent condensation with aldehydes affords the corresponding 7-arylidene derivatives.¹⁷¹



¹⁷¹ N. A. E. Kassab, S. O. A. Alla, and H. A. R. Ead, *Z. Naturforsch., Teil B* **31**, 853 (1976).

3. Cyclization between the 4,5-Positions

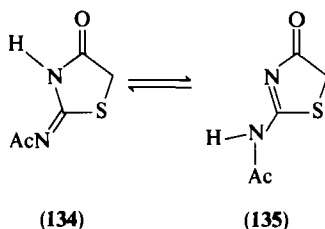
Reaction of formylhydrazine and **132** occurs with subsequent pyrazole ring closure to give **133** [Eq. (40)].¹²³



IV. Spectral Aspects

A. X RAY

In view of the widespread application of thiazolidinones to physiological and industrial needs, the X-ray analyses of **2**,¹⁷² **13b** (R = Ph; R' = H),¹⁷³ **12b** (R = Ph; R' = R'' = H),¹⁷⁴ **12b** (R = R' = R'' = H),¹⁷⁵ and **12b** (R = R'' = Ph; R' = Me)¹⁷⁶ have been accomplished. The 2-acetyl derivative of 2-amino-4-thiazolidine possesses structure **134** in the crystal state, but in solution both tautomeric forms are present, as established by spectral data.¹⁷⁷



¹⁷² G. R. Form, E. S. Raper, and R. C. Downie, *Acta Crystallogr., Sect. B* **31**, 2181 (1975).

¹⁷³ B. W. Matthews, *Acta Crystallogr.* **17**, 1413 (1964).

¹⁷⁴ L. A. Plastas and J. M. Stewart, *Chem. Commun.* p. 811 (1969).

¹⁷⁵ R. V. Ananthamurthy, M. R. Udupa, and B. V. R. Murthy, *Z. Kristallogr., Kristallgeom., Kristallphys., Kristallchem.* **137**, 316 (1973); **142**, 356 (1976); **144**, 259 (1977); R. V. A. Murthy and B. V. R. Murthy, *Cryst. Struct. Commun.* **4**, 117 (1975).

¹⁷⁶ R. Bally and J. P. Mornon, *C. R. Hebd. Seances Acad. Sci., Ser C* **275**, 933 (1972); *Acta Crystallogr., Sect B* **29**, 1160 (1973).

¹⁷⁷ E. M. Peresleni, Yu. N. Sheinker, and N. P. Zosimova, *Zh. Fiz. Khim.* **39**, 926 (1965).

B. INFRARED SPECTRA

Numerous studies of the infrared spectral data have been reported, especially in connection with the problem of the tautomeric equilibria of substituted 4-thiazolidinones. Particular references to substituted derivatives of **2**^{109,121,178,179} and **3**^{12,126,132,179,180} are of interest.

C. ULTRAVIOLET SPECTRA

An alternative approach to information about tautomeric equilibria with these compounds is via ultraviolet data. Ultraviolet data for substituted **2**^{129,143,181,182} and **3**^{12,126,132,179-182} have been reported. In the condensation of thiourea and α -haloacetic acids, the main absorption maximum at 241–249 nm is preserved due to the polar structures of pseudothiohydantoins.¹⁸¹ Generally, in the UV spectra of substituted **2** and **3**, the amide bond is weak.¹⁸¹

D. NUCLEAR MAGNETIC RESONANCE SPECTRA

Very limited proton magnetic resonance data have been reported, since generally PMR provides little information about the heterocyclic ring.^{12,183}

- ¹⁷⁸ C. Fayat, *C. R. Hebd. Seances Acad. Sci., Ser. C* **264**, 1811 (1967); R. S. Lebedev and V. I. Yamenko, *Izv. Vyssh. Uchebn. Zaved., Fiz.* **12**, 64 (1969); R. S. Lebedev, V. I. Yakimenko, N. I. Afcinas'eva, and A. V. Bobrov, *ibid.* **14**, 127 (1971); R. S. Lebedev and A. V. Korshunov, *ibid.* p. 138; R. S. Lebedev, *ibid.* **15**, 142 and 148 (1972); A. V. Korshunov, V. E. Volkov, R. S. Lebedev, and A. E. Koralev, *Vopr. Mol. Spektrosk.* p. 9 (1974); R. S. Lebedev, V. N. Yukhimets, V. I. Yakimenko, A. N. Gromnitski, and N. N. Golokhvastov, *ibid.* p. 63; C. Fayat and A. Foucaud, *Bull. Soc. Chim. Fr.*, p. 987 (1971); C. Cogrossi, *Spectrochim. Acta, Part A* **28**, 855 (1972); N. M. Turkevich, A. A. Kuzhelyuh, A. V. Babak, L. T. Emchik, and L. Ya. Ladnava, *Izv. Vyssh. Uchebn. Zaved., Khim. Tekhnol.* **15**, 859 (1972); A. A. Kuzhelyuh, N. M. Turkevich, B. V. Babak, and L. T. Emchik, *ibid.* **16**, 1516 (1973); L. Narvor, J. Lauransan, and P. Saumagne, *Can. J. Chem.* **51**, 433 (1973); K. A. V'yunov, A. I. Ginak, and E. G. Sochilin, *Zh. Prikl. Spektrosk.* **25**, 865 (1976).
- ¹⁷⁹ N. A. Borisevich and N. N. Khovratovich, *Zh. Prikl. Spektrosk.* **7**, 538 (1967); S. M. Ramsh, K. A. V'yunov, A. I. Ginak, and E. G. Sochilin, *Khim. Geterotsikl. Soedin.* p. 775 (1972).
- ¹⁸⁰ A. S. Mitra and M. K. Rout, *J. Indian Chem. Soc.* **40**, 993 (1963); N. N. Khovratovich and I. I. Chizhevskaya, *Khim. Geterotsikl. Soedin.* **3**, 637 and 642 (1967); **5**, 52 (1969); P. J. Taylor, *Spectrochim. Acta Part A* **26**, 153 and 165 (1970); S. M. Ramsh, G. S. Antonova, A. I. Ginak, N. A. Smorygo, and E. G. Sochilin, *Zh. Org. Khim.* **11**, 1759 (1975).
- ¹⁸¹ N. M. Turkevich and A. F. Minka, *Zh. Obshch. Khim.* **35**, 884 (1965).
- ¹⁸² S. N. Baranov and A. P. Grishchuk, *Zh. Obshch. Khim.* **32**, 1938 (1962); M. L. Girard and C. Dreux, *Bull. Soc. Chim. Fr.* p. 3477 (1968); A. M. Comrie, *J. Chem. Soc.* p. 3474 (1964).
- ¹⁸³ T. Takahashi, *Tetrahedron Lett.* p. 565 (1964).

The structures of isomeric 2-methylenethiazolidin-4-ones have been ascertained by NMR analysis.⁶⁹ Recently, several papers on ¹³C-NMR spectra of 4-thiazolidinones have been reported.¹⁸⁴

E. MASS SPECTRA

High and low resolution mass spectral data are available for several 2-thiazolidinones¹⁸⁵ and 2-methylene thiazolidin-4-ones.⁷⁰ Very limited mass spectral data are available for these compounds.

V. Physical Aspects

A. pK_a AND TAUTOMERIC EQUILIBRIA

From the pK_a values, the following sequence of 2-substituted 4-thiazolidinones with respect to the degree of acidity is $5 > 2 > 3$.¹⁸⁶ The opening of the thiazolidinone ring leads to an increase in acidity, but does not affect the activity sequence of the substituents.¹⁸⁶ The acidity of a series of substituted 5-benzylidene-2,4-thiazolidinediones has been investigated; the entropy, enthalpy, and free energy of ionization have been calculated.¹⁸⁷ Potentiometric determination of the tautomeric equilibrium constants of various 4-thiazolidinones has been reported.¹⁸⁸

B. POLAROGRAPHIC STUDIES

The reduction mechanism of four 2-(arylimino)-4-thiazolidiones in Britton–Robinson buffer was studied.^{8,189} In the pH range 2–7.3, there

¹⁸⁴ R. S. Dewey, E. F. Schoenewaldt, H. Joshua, W. J. Paleveda, H. Schwam, H. Barkemeyer, B. H. Arison, D. F. Veber, R. G. Denkwalker, and R. Hirschmann, *J. Am. Chem. Soc.* **90**, 3254 (1968); U. Vögeli, W. von Philipsborn, K. Nagarajan, and M. D. Nair, *Helv. Chim. Acta* **61**, 607 (1978).

¹⁸⁵ R. C. Dougherty, R. L. Flotz, and L. B. Kier, *Tetrahedron* **26**, 1989 (1970).

¹⁸⁶ E. V. Vladzimirskaya and Yu. M. Pashkevich, *Zh. Obshch. Khim.* **33**, 3149 (1963).

¹⁸⁷ K. A. V'yunov, I. M. Mogileva, A. I. Ginak, and E. G. Sochilin, *Zh. Org. Khim.* **7**, 1733 (1971).

¹⁸⁸ M. L. Girard and C. Dreux, *C. R. Hebd. Seances Acad. Sci.* **260**, 2225 (1965); H. Najer, J. Armand, J. Menin, and N. Voronine, *ibid.* **260**, 4343 (1965); G. S. Antonova, S. M. Ramsh, A. I. Ginak, and E. G. Sochilin, *Zh. Org. Khim.* **11**, 1970 (1975).

¹⁸⁹ Yu. V. Svetkin, Kh. F. Bikbaeva, and R. I. Khusnutdinov, *Zh. Obshch. Khim.* **41**, 1904 (1971).

occurs irreversible two-electron reduction of the imino group with prior protonation.¹⁸⁹ Polymethylene bis(2-imino-4-thiazolidinones) have also been electrochemically reduced.⁸¹

C. COMPLEXATION STUDIES

Ni(II),¹⁹⁰ Co(II),¹⁹¹ Cu(I),⁵ Ag(I),⁵ Au(I),⁵ Zn(II),⁵ Cd(II),⁵ Hg(II),⁵ and Hg(I)⁵ complexes of **3** have been prepared and characterized. Dione **2** forms complexes with Sn(IV), Ti(IV), and Fe(II); infrared data support the carbonyl oxygen as the donor site.¹⁹²

VI. Utilitarian Aspects

Over the years, 4-thiazolidinones have been synthesized for a wide range of industrial, pharmaceutical, and biological purposes. The following list does not include the patent literature, because of space limitations. Thiazolidinone derivatives have been shown to exhibit fungicidal,^{10,17,20-24,27,30,36-39,97,103,145} pesticidal,^{10,11,19,130} antitubercular,^{23,48,49,118} anticonvulsant,^{32,41,48,52,56,151} local anesthetic,¹⁴² nematocidal,¹⁰ bactericidal,^{17,20-24,50,95,96,103,127,130,147} antiviral,^{46,49} herbicidal,⁵¹ antiprotozoal,¹⁰³ and hypoglycemic activity,¹²⁸ and possible antimycotic properties;¹³¹ they may also act as potential antiradiation¹⁶⁷ and chemotherapeutic¹²⁷ agents.

¹⁹⁰ P. P. Singh and U. P. Shukla, *Inorg. Chim. Acta* **7**, 493 (1973).

¹⁹¹ M. R. Udupa, G. Krishnan, and G. Aravamudan, *Inorg. Nucl. Chem. Lett.* **9**, 491 (1973).

¹⁹² P. P. Singh, O. P. Agrawal, and A. K. Gupta, *Inorg. Chim. Acta* **18**, 19 (1976).

Ring Synthesis of Heteroaromatic Nitro Compounds

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I. Introduction

The theme of this review is the construction of heteroaromatic nitro compounds from open-chain nitro-containing precursors. Such synthetic procedures offer two specific advantages over nitration of a preformed heterocycle: (i) emergence of novel substitution patterns, and (ii) retention of substituents which might be vulnerable to destruction by the reagents or conditions employed for nitration.

In view of the usefulness of a variety of nitro-heterocycles, especially as antiprotozoal and antibacterial agents, some of these otherwise inaccessible derivatives might exhibit advantageous therapeutic properties.

Many different types of aliphatic nitro compounds have been used in such syntheses. These vary in their oxidation state, the presence or absence of other functional groups, etc. With proper choice of the complementary reactant, union between the two moieties results in the formation of a heteroaromatic compound with the nitro group occupying a predetermined location. For convenience, we have classified these nitro-containing synthons as belonging to types 1, 2, or 3 depending on whether they contribute one, two, or three carbon atoms to the resultant heterocyclic nucleus. However, this classification cannot be rigorously interpreted, since most of the type 2 and type 3 reagents are themselves prepared from nitromethane. Listed below are some of the more common nitro-containing synthons:

Type 1: Nitromethane, bromonitromethane

Type 2: Trichloronitroethylene, nitroenamines, 1,1-bis(methylmercapto)-2-nitroethylene, nitroacetic esters

Type 3: Nitromalonaldehyde, nitromalonic esters, ethoxymethylenenitroacetic ester

This review covers the literature reported in Chemical Abstracts up to Volume 87 and in the common primary journals published until the end of 1977.

II. Synthesis of Five-Membered Nitro-Heterocycles

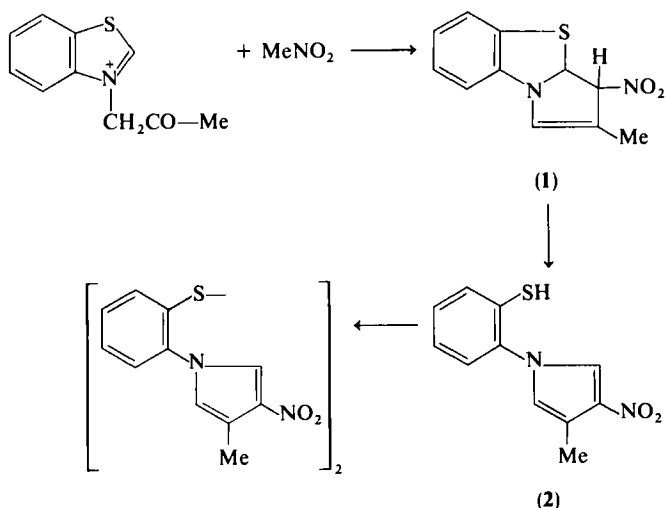
A. RINGS WITH ONE HETEROATOM

1. Nitropyrroles

2-Nitropyrroles do not seem to have been made by cyclization procedures, but several such routes have been described for 3-nitropyrroles. The nitro-containing synthon may be of type 1, 2, or 3. In addition, there is one report of the synthesis of a 3,4-dinitropyrrole by direct ring closure.

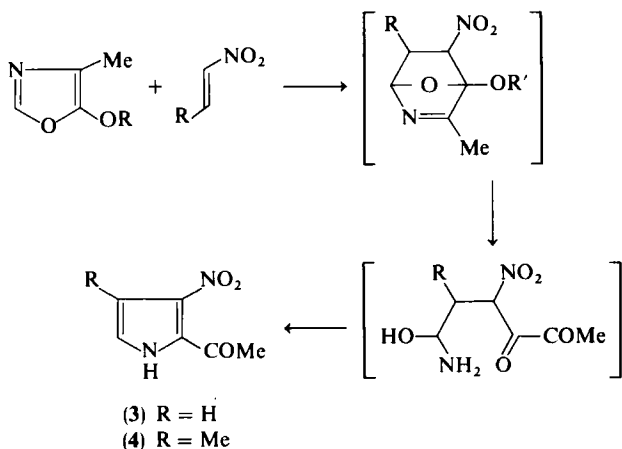
a. 3-Nitropyrroles. The ylid derived from *N*-acetylbenzthiazolium bromide reacts with nitromethane in the presence of base to produce the 3-nitropyrrole derivative **2**¹ by cleavage of the C—S bond in the intermediate **1**. The thiol group is finally oxidized in air to the disulfide (Scheme 1).

¹ W. Kiel and F. Kröhnke, *Chem. Ber.* **105**, 3709 (1972).



SCHEME 1

Reaction of a 5-alkoxy-4-methyloxazole with nitroethylene in benzene at -4° , followed by acid hydrolysis, leads to the 3-nitropyrrole **3** (57%).² 1-Nitropropene similarly gave 2-acetyl-4-methyl-3-nitropyrrole (**4**).³ The initial Diels-Alder adduct under acidic conditions is transformed as in Scheme 2.

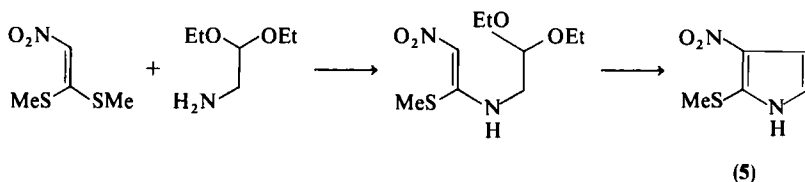


SCHEME 2

² S. V. Stepanova, S. D. L'vova, A. B. Belikov, and V. I. Gunar, *Zh. Org. Khim.* **13**, 889 (1977); *Chem. Abstr.* **87**, 53135 (1977).

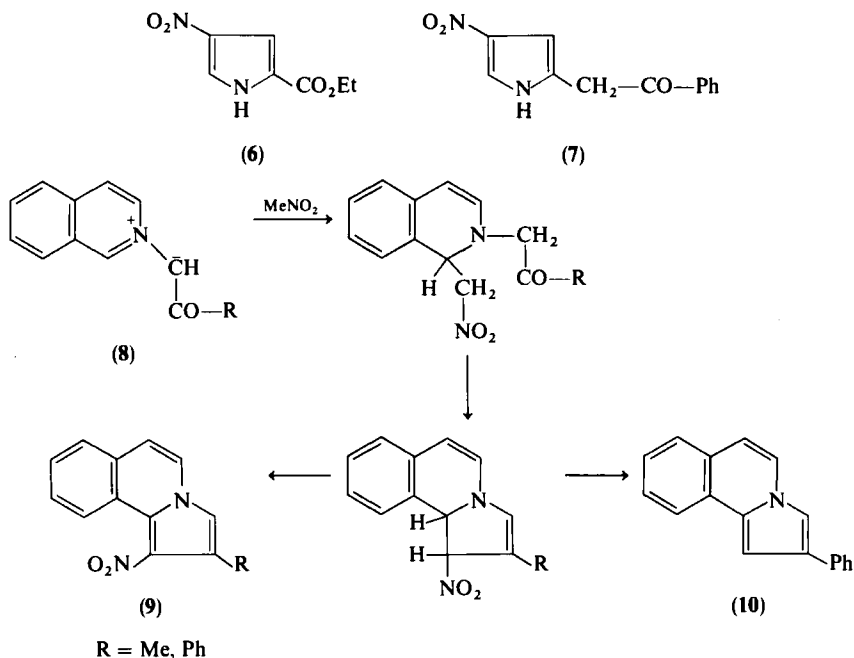
³ S. V. Stepanova, S. D. L'vova, B. S. El'yanov, and V. I. Gunar, *Khim. Farm. Zh.* **11**, 92 (1977).

Recently, 1,1-bis(methylmercapto)-2-nitroethylene has been reacted with aminoacetaldehyde diethylacetal and the product cyclized by dry HCl in ether to give 2-methylmercapto-3-nitropyrrole (**5**) (Scheme 3).⁴



SCHEME 3

Nitromalonaldehyde reacts with ethyl glycinate^{5,6} and β -aminopropiophenone⁷ in the presence of alkali to yield **6** (66%) and **7** (30%), respectively.⁵⁻⁸



SCHEME 4

⁴ A. Kumar, H. Ila, and H. Junjappa, *Chem. Commun.* p. 593 (1976).

⁵ W. J. Hale and W. V. Hoyt, *J. Am. Chem. Soc.* **37**, 2538 (1915).

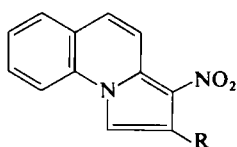
⁶ K. J. Morgan and D. P. Morrey, *Tetrahedron* **22**, 57 (1966).

⁷ W. J. Hale and E. C. Britton, *J. Am. Chem. Soc.* **41**, 1020 (1919).

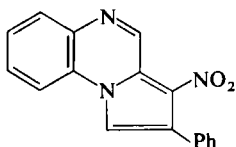
⁸ W. J. Hale and E. M. Honan, *J. Am. Chem. Soc.* **41**, 770 (1919).

Many annellated 3-nitropyrroles have been prepared by the reaction of ylids, generated from a variety of heterocycles, with nitromethane.¹ The sequence of steps involves protonation of the ylid by nitromethane, addition of the anion $^{-}\text{CH}_2\text{NO}_2$ to the iminium system, cyclization on the carbonyl, dehydration, and finally dehydrogenation. Thus, the isoquinolinium ylids **8** react with nitromethane in the presence of base to give 1-nitropyrrolo-[2,1-*a*]isoquinolines (**9**) in about 20% yield (Scheme 4). A side reaction is the loss of nitrous acid from the intermediate, to give **10**.

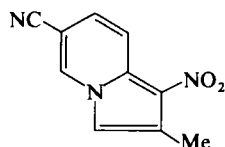
Quinolinium ylids react similarly to give 3-nitropyrrolo[1,2-*a*]quinolines (**11**) (40–45%) and *N*-phenacylquinoxalinium bromide gives 3-nitro-2-phenylpyrrolo[1,2-*a*]quinoxaline **12** (41%).¹ Neither *N*-acetyl- nor *N*-phenacylpyridinium bromide undergoes cyclization with nitromethane. However, when the pyridine ring carries a nitrile group at the 3-position, a 1-nitroindolizine (**13**) is formed.¹



(11)

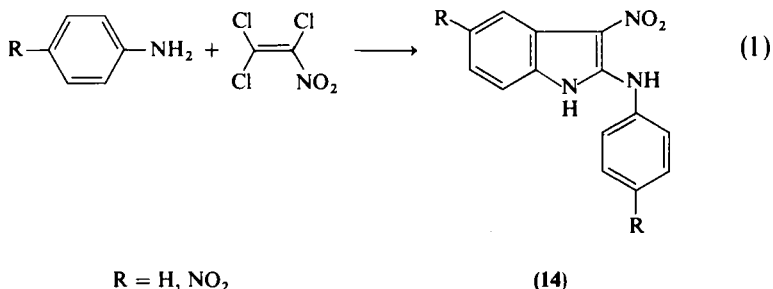


(12)



(13)

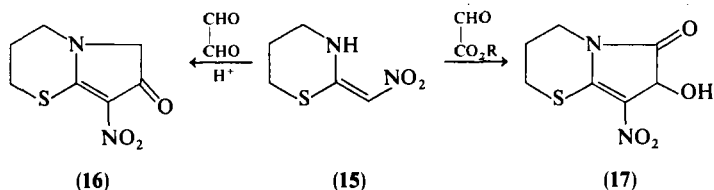
Russian workers have recently devised a synthesis of 2-anilino-3-nitroindoles (**14**) (> 75%) by reacting aromatic amines with trichloronitroethylene [Eq. (1)].⁹



Condensation of the nitroenamine **15** with glyoxal and glyoxylic acid results in the formation of the pyrrolo[2,1-*b*][1,3]thiazine derivatives **16**

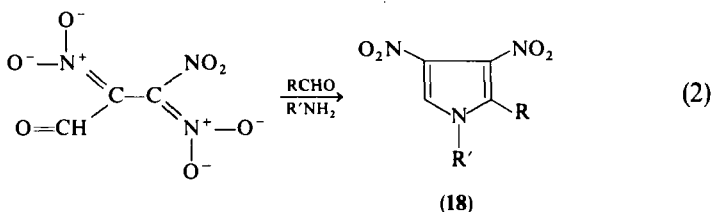
⁹ V. A. Buevich, V. V. Rudchenko, and V. V. Perekalin, *Khim. Geterotsikl. Soedin.* p. 1429 (1976); *Chem. Abstr.* **86**, 72357 (1977).

and 17, respectively (Scheme 5).^{10,11} In their enolic forms, these would constitute aromatic nitropyrroles. However, simpler pyrrole derivatives with similar structural features exist in the oxo forms.¹²



SCHEME 5

b. 3,4-Dinitropyrroles. These have been synthesized from the dipotassium salt of trinitropropionaldehyde by reaction with an aliphatic aldehyde and a primary amine in the presence of a little ammonia [Eq. (2)].^{13,14} The yields are generally 10–20%, but 40% was reported, for one case (18; R = H, R' = Me).



2. Nitrofurans

Both 2- and 3-nitrofurans with additional substituents on the available positions of the furan ring have been synthesized by cyclization procedures. The nitro-containing reagents are of type 1 or 2. No type 3 reagent seems to have been used for the synthesis of nitrofurans or condensed nitrofurans.

¹⁰ J. E. Powell, U.S. Patent 4,033,955 (1977); *Chem. Abstr.* **87**, 117889 (1977).

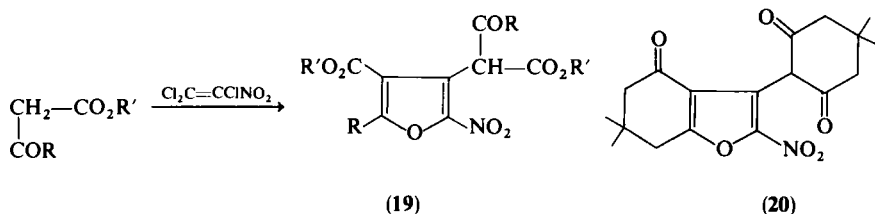
¹¹ C. H. Tieman, U.S. Patent 4,033,954 (1977); *Chem. Abstr.* **87**, 102367 (1977).

¹² J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, **Suppl.** **1**, 244 and 246 (1976).

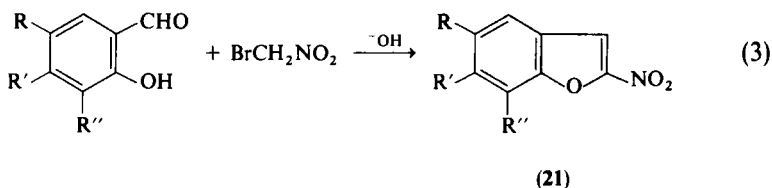
¹³ S. S. Novikov, E. N. Safonova, and V. M. Belikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 1053 (1960); *Chem. Abstr.* **54**, 24641 (1960); E. Baltazzi and L. I. Krimen, *Chem. Rev.* **63**, 534 (1963).

¹⁴ S. S. Novikov and V. M. Belikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 1098 (1959); *Chem. Abstr.* **54**, 1487 (1960).

a. 2-Nitrofurans. The reaction of trichloronitroethylene with methyl benzoylacetate and other β -ketoesters leads to the 2-nitrofurans **19** (40–50%).^{15–17} Acid hydrolysis (HCl in HOAc) removes the side-chain ester group. Substitution of dimedone for the β -ketoester leads to **20**.



2-Nitrobenzofurans (**21**) have been obtained by the condensation of substituted salicylaldehydes with bromonitromethane,^{18,19} a versatile reagent useful for the synthesis of various other nitro-heterocycles. The yields however, are variable (5–52%) [Eq. (3)].



b. 3-Nitrofurans. Substituted 3-nitrofurans (**22**) have been prepared (~45%) by direct ring closure from benzaldehyde, aniline hydrochloride, and the sodium salt of 2-nitro-3-oxosuccinaldehydic acid.²⁰ Analogous reactions with *p*-anisaldehyde and *p*-chlorobenzaldehyde have been reported. Two molecules of benzaldehyde are incorporated, as outlined in Scheme 6.

¹⁵ L. I. Deiko, V. A. Buevich, V. S. Grineva, and V. V. Perekalin, *Khim. Geterotsikl. Soedin.* p. 1148 (1975); *Chem. Abstr.* **84**, 17045 (1976).

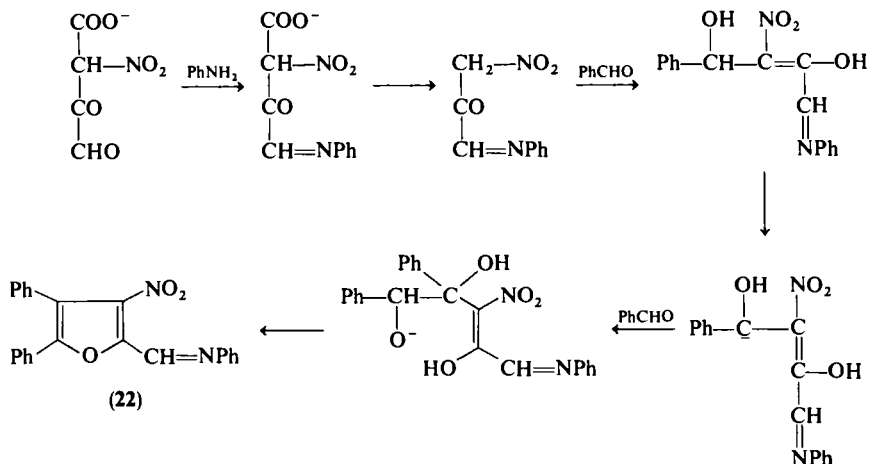
¹⁶ V. A. Buevich, L. I. Deiko, and V. V. Perekalin, *Khim. Geterotsikl. Soedin.* p. 311 (1977); *Chem. Abstr.* **87**, 22904 (1977).

¹⁷ V. A. Buevich, L. I. Deiko, and V. V. Perekalin, *Zh. Org. Khim.* **13**, 972 (1977); *Chem. Abstr.* **87**, 68047 (1977).

¹⁸ R. Royer, P. Demerseman, and L. René, *Bull. Soc. Chim. Fr.* p. 3740 (1970); R. Royer, J. P. Buisson, and L. René, *ibid.* p. 4158 (1972); R. Royer, L. René, R. Cavier, and J. Lemoine, *Eur. J. Med. Chem.—Chim. Ther.* **12**, 455 (1977).

¹⁹ Y. Oishi, Y. Doi, K. Nishi, T. Nakajima, M. Ikemoto, and T. Nakanishi, *Japan Kokai* 77/73,859; *Chem. Abstr.* **87**, 167868 (1977).

²⁰ D. S. James and P. E. Fanta, *J. Org. Chem.* **28**, 390 (1963).

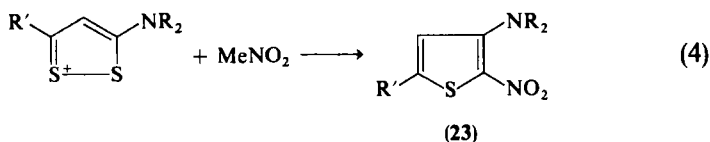


SCHEME 6

3. Nitrothiophenes

Both 2- and 3-nitrothiophenes have been synthesized by direct cyclization. While the former have been prepared with the help of type 1 reagents alone (nitromethane, bromonitromethane), the preparation of the latter has involved reagents of types 2 and 3. A synthesis in which both reactants carry nitro groups has led to 2,4-dinitrothiophenes.

a. 2-Nitrothiophenes. 3-Amino-1,2-dithiolium salts react with nitromethane in methanol at 20° in the presence of sodium methoxide to form 3-amino-2-nitrothiophenes (23) [Eq. (4)].²¹



Phenylpropionic thioanilide and bromonitromethane in presence of triethylamine give the 2-nitrothiophene **24**.²² Evidently, initial *S*-alkylation is followed by addition of the acidic methylene to the triple bond as in Eq. (5).

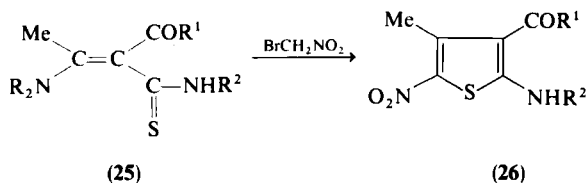
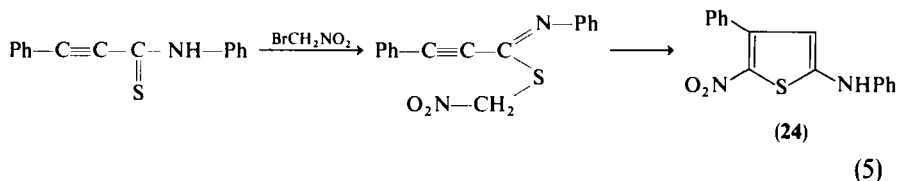
Similarly, the enamine-isothiocyanate adducts (25) react with bromonitromethane to form the 2-nitrothiophene derivatives **26**.²³ Yields are

²¹ B. Bartho, J. Faust, R. Pohl, and R. Mayer, *J. Prakt. Chem.* **318**, 221 (1976).

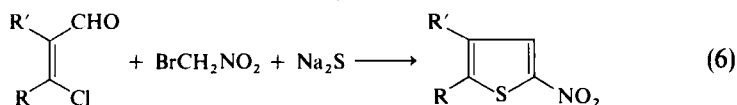
²² W. Ried and L. Kaiser, *Synthesis* p. 120 (1976).

²³ S. Rajappa and B. G. Advani, *Indian J. Chem.* **16**, 752 (1978).

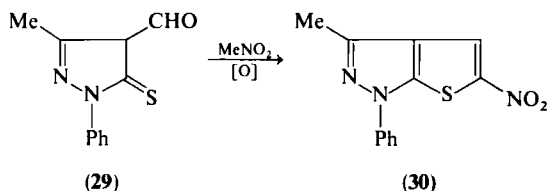
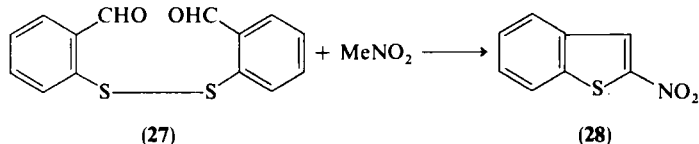
moderate when the R groups are alkyl. When R = H, oxidative cyclization becomes a competing side reaction.



β -Chloro- α,β -unsaturated aldehydes react with sodium sulfide and bromonitromethane to give 2-nitrothiophenes [Eq. (6)].²⁴



Reaction of 2,2'-diformyldiphenyldisulfide (27) with nitromethane in the presence of triethylamine gives 2-nitrobenzothiophene (28) (29%).²⁵ Addition of benzoyl peroxide (0.5 mol) increases the yield to 77%. A similar reaction of the pyrazole derivative 29 leads to the thieno[3,2-d]pyrazole 30.²⁵

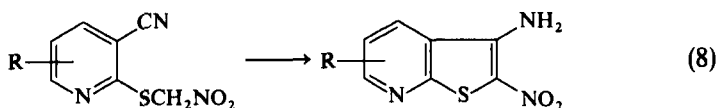
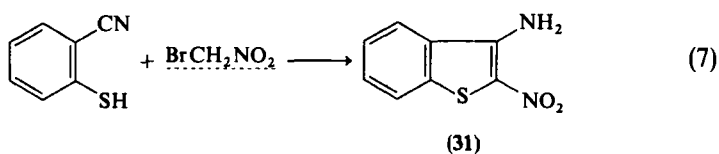


Bromonitromethane has also been used to produce a 2-nitrobenzothiophene; *o*-cyanothiophenol with bromonitromethane in aqueous sodium

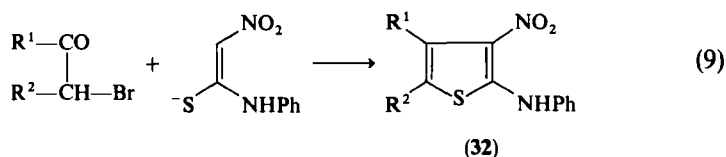
²⁴ P. Cagniant and G. Kirsch, *C.R. Hebd. Seances Acad. Sci., Ser. C* **281**, 35 (1975); *Chem. Abstr.* **83**, 178681 (1975).

²⁵ K. J. Brown and O. Meth-Cohn, *Tetrahedron Lett.* p. 4069 (1974).

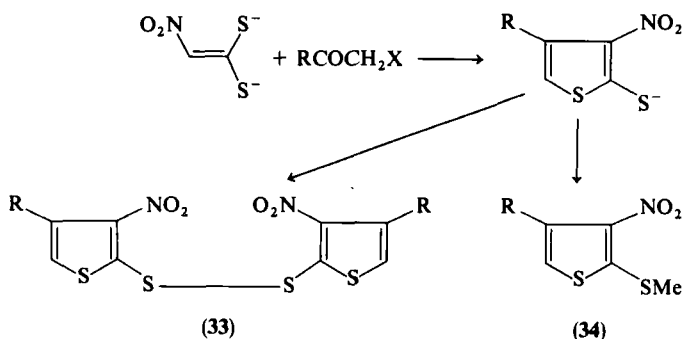
hydroxide gives 3-amino-2-nitrobenzo[*b*]thiophene (31) [Eq. (7)].²⁶ The reaction has been extended to the pyridine series [Eq. (8)].²⁷



b. 3-Nitrothiophenes. The sodium salt of 1-anilino-1-mercapto-2-nitroethylene reacts with α -haloketones to form 2-anilino-3-nitrothiophenes 32 [Eq. (9)].²⁸



Similarly, treatment of 2-nitroethylene-1,1-dithiolate with α -halocarbonyl compounds results in derivatives of 3-nitrothiophene-2-thiol.²⁹ The products are isolated either by oxidation to the disulfides (33) or by *S*-methylation (34) (Scheme 7).



SCHEME 7

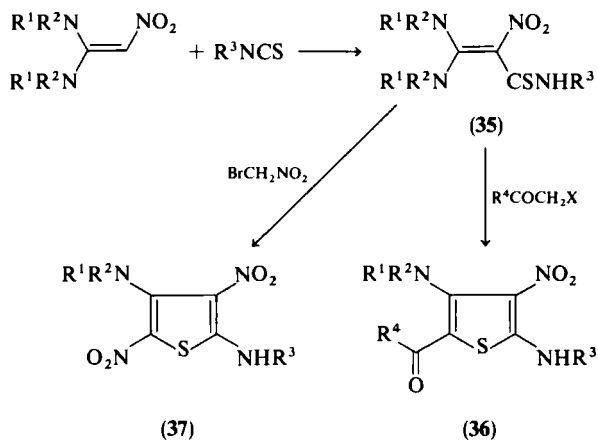
²⁶ D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C* p. 3903 (1971).

²⁷ R. Niess and H. Eilingsfeld, German Patent 2,241,717 (1974): *Chem. Abstr.* **80**, 146133 (1974).

²⁸ H. Schäfer and K. Gewald, *Z. Chem.* **15**, 100 (1975).

²⁹ L. Henrikson and H. Autrup, *Acta Chem. Scand.* **24**, 2629 (1970).

In these two syntheses, the α -haloketone supplies two carbon atoms to the thiophene ring. In a different approach, the α -haloketone provides only one of the carbon atoms of the ring, the other three carbon atoms being derived from the nitro-containing reagent. Nitroketeneaminals are first treated with aliphatic or aromatic isothiocyanates to form the adducts **35**. Reaction with α -haloketones then leads to the 5-acyl-3-nitrothiophenes **36** (20–50%) (Scheme 8).^{30,31}



SCHEME 8

c. 2,4-Dinitrothiophenes. Reaction of the nitroketeneaminal-isothiocyanate adducts (**35**) with bromonitromethane has given the 2,4-dinitrothiophenes **37** in moderate yields.²³

4. Nitroselenophenes and Nitrotellurowhenes

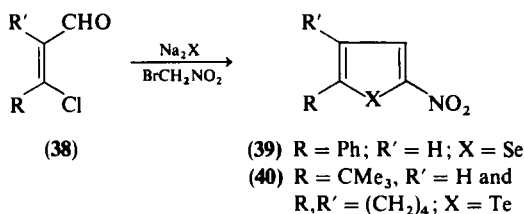
In an extension of their synthesis of 2-nitrothiophenes, Cagniant and co-workers have prepared 2-nitroselenophenes and -tellurowhenes by similar procedures.^{32,33} Thus, the β -chloro- α,β -unsaturated aldehyde **38** ($R = Ph$; $R' = H$) reacts with bromonitromethane and sodium selenide to form the 2-nitroselenophene **39**. Similarly, with sodium telluride and bromonitromethane, chlorovinylaldehydes yield 2-nitrotellurowhenes (**40**).

³⁰ S. Rajappa, B. G. Advani, and R. Sreenivasan, *Synthesis* p. 656 (1974).

³¹ S. Rajappa and R. Sreenivasan, *Indian J. Chem.*, **15**, 301 (1977).

³² P. Cagniant, P. Perin, and G. Kirsch, *C.R. Hebd. Seances Acad. Sci., Ser. C* **278**, 1201 (1974); *Chem. Abstr.* **81**, 63435 (1974).

³³ P. Cagniant, R. Close, G. Kirsch, and D. Cagniant, *C.R. Hebd. Seances Acad. Sci., Ser. C* **281**, 187 (1975); *Chem. Abstr.* **84**, 43758 (1976).

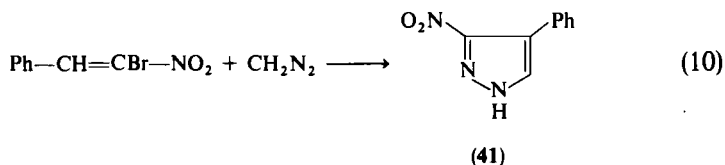


B. RINGS WITH TWO HETEROATOMS

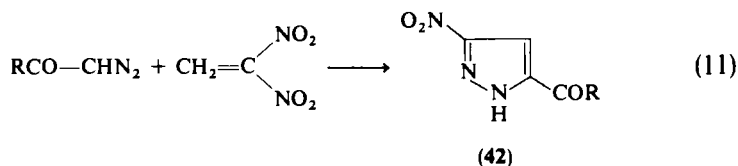
1. Nitropyrazoles

a. 3-Nitropyrazoles. The nitro-containing moiety usually contributes two or three carbon atoms to the pyrazole ring in syntheses of 3-nitropyrazoles. No type I reagent seems to have been used for this purpose.

β -Bromo- β -nitrostyrene reacts with diazomethane to give, in 42% yield, the 3-nitropyrazole **41** [Eq. (10)].³⁴ Higher yields (73%) are reported when the intermediate pyrazoline is dehydrobrominated with sodium bicarbonate.



1,1-Dinitroethylene reacts with α -diazoketones to give 5-acyl-3-nitropyrazoles (**42**) by loss of one molecule of nitrous acid from the intermediate [Eq. (11)].³⁵

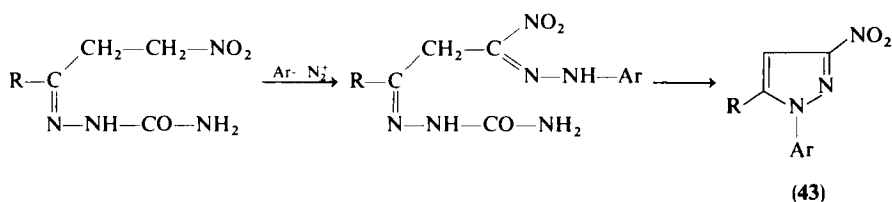


Semicarbazones of β -nitrocarbonyl compounds have been coupled with aryl diazonium salts and the resulting hydrazones cyclized by acid to the 3-nitropyrazoles **43** (Scheme 9).³⁶

³⁴ W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.* **73**, 4664 (1951).

³⁵ A. L. Fridman, F. A. Gabimov, and V. D. Surkov, *Zh. Org. Khim.* **8**, 2457 (1972); *Chem. Abstr.* **78**, 83543 (1973).

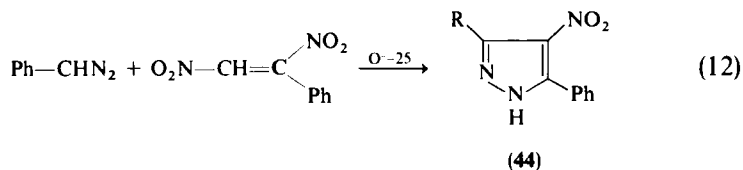
³⁶ R. Fusco and S. Rossi, *Rend. Ist. Lomb. Sci. Lett.* **93**, 334 (1959); R. Fusco, *Chem. Heterocycl. Compd.* **22**, 93 (1967).



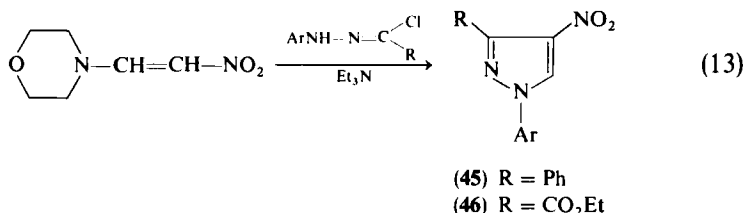
SCHEME 9

b. 4-Nitropyrazoles. Several type 2 and type 3 reagents have been used to prepare 4-nitropyrazoles. Here too, type 1 reagents do not seem to have found any application.

Phenyldiazomethane reacts with α,β -dinitrostyrene under mild conditions to produce 3,5-diphenyl-4-nitropyrazole (**44**) [Eq. (12)].³⁷



Reaction of 1-morpholino-2-nitroethylene with α -chlorohydrazone and triethylamine has given 4-nitropyrazoles (**45**, **46**) in low yields [Eq. (13)].³⁸



Several reports are available on the condensation of nitromalonaldehyde with hydrazines to give 4-nitropyrazole derivatives (**47**) [Eq. (14)].³⁹⁻⁴¹ The reaction of sodio-nitromalonaldehyde with aminoguanidine in the presence of acid directly yields 1-guanyl-4-nitropyrazole (**48**; R = C(NH)NH₂).^{42,43}

³⁷ F. A. Gabitov, O. B. Kremleva, and A. L. Fridman, *Zh. Org. Khim.* **13**, 1117 (1977); *Chem. Abstr.* **87**, 84885 (1977).

³⁸ D. Pocar, S. Maiorana, and P. Dalla Croce, *Gazz. Chim. Ital.* **98**, 949 (1968).

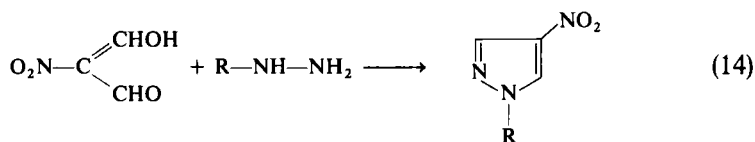
³⁹ H. B. Hill and J. Torrey, *Am. Chem. J.* **22**, 89 (1899).

⁴⁰ D. Dal Monte, A. Mangini, and R. Passerini, *Gazz. Chim. Ital.* **86**, 797 (1956).

⁴¹ I. L. Finar and R. J. Hurlock, *J. Chem. Soc.* p. 3024 (1957).

⁴² F. L. Scott and J. Reilly, *Chem. Ind. (London)* p. 907 (1952).

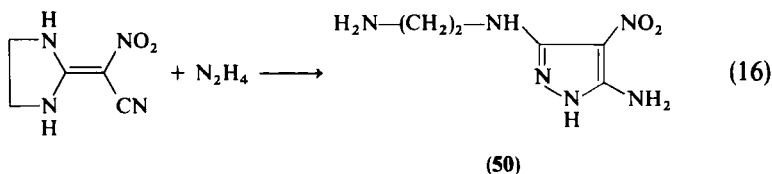
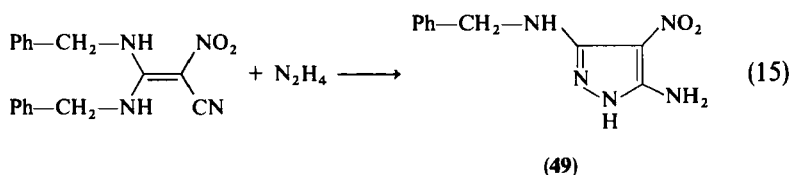
⁴³ M. Moreau, I. Karadavidoff, and M. Stjerpanovic, *Ger. Offen.* 2,557,514 (1976); *Chem. Abstr.* **85**, 123918 (1976).



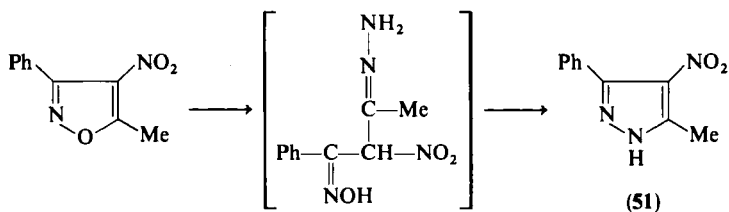
(47)

(48) $\text{R} = \text{C}(\text{NH})\text{NH}_2$

3,3-Diamino-2-nitroacrylonitriles react with hydrazine to give 3,5-diamino-4-nitropyrazoles (**49**, **50**) in high yields.⁴⁴ The reaction has been carried out with compounds containing identical amino groups [Eq. (15)], or with cyclic compounds derived from ethylenediamine [Eq. (16)].



The conversion of 4-nitroisoxazoles into 4-nitropyrazoles (**51**) by hydrazine probably involves the nitro-oximino hydrazone (Scheme 10).⁴⁵⁻⁴⁷



SCHEME 10

4-Nitro-3-pyrazolones (**52**) have been prepared recently by reaction of ethyl- β -ethoxy- α -nitroacrylate and -crotonate with hydrazine and its derivatives [Eq. (17)].⁴⁸

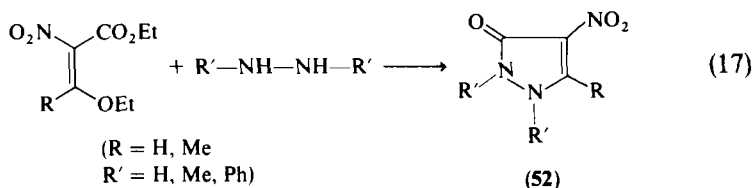
⁴⁴ S. Rajappa and B. G. Advani, *Indian J. Chem.* **15**, 890 (1977).

⁴⁵ C. Musante, *Gazz. Chim. Ital.* **72**, 537 (1942); *Chem. Abstr.* **38**, 4597 (1944).

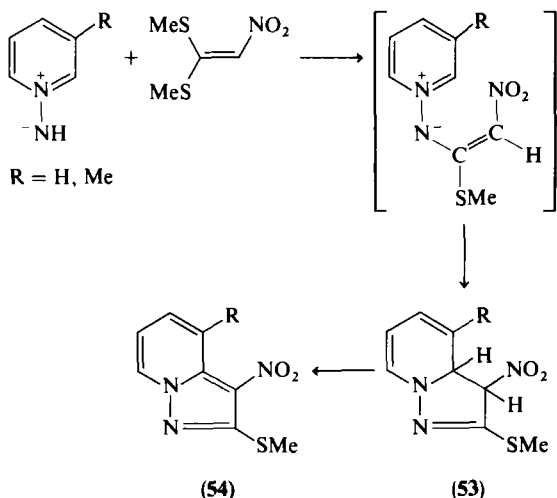
⁴⁶ C. Musante, *Gazz. Chim. Ital.* **73**, 355 (1943); *Chem. Abstr.* **41**, 1223 (1947).

⁴⁷ A. Quilico, *Chem. Heterocycl. Compd.* **17**, 48 and 49 (1962).

⁴⁸ O. S. Wolfbeis, *Synthesis* p. 136 (1977).



Condensed 4-nitropyrazoles have been produced from pyridinium *N*-imines and 1,1-bis(methylmercapto)-2-nitroethylene; 2-methylthio-1-nitropyrzolo[1,5-*a*]pyridines (54) (40–60%) are so obtained.⁴⁹ After the electrocyclic transformation, the intermediate 53 does not lose the elements of nitrous acid, but rather undergoes dehydrogenation to yield the observed products (Scheme 11). Isoquinolinium *N*-imine gives 2-methylthio-1-nitropyrzolo[5,1-*a*]isoquinoline similarly.⁴⁹



SCHEME 11

2. Nitroisoxazoles

3-Nitro- and 4-nitro-, but no 5-nitroisoxazoles, have been prepared by direct cyclization procedures.

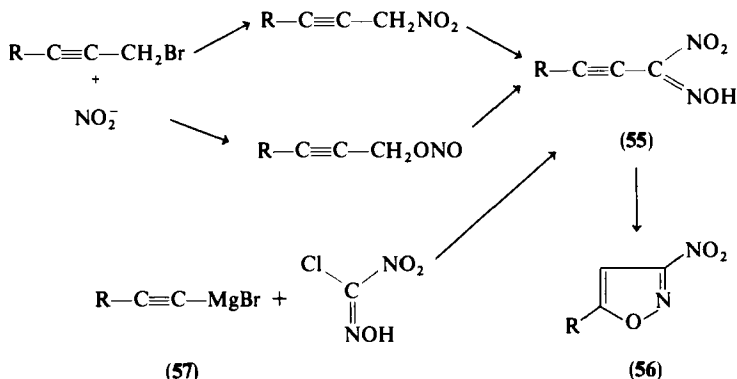
a. 3-Nitroisoxazoles. Substituted propargyl bromides and sodium nitrite in DMF give 3-nitroisoxazoles 56 (20–60%).^{50,51} The reaction is

⁴⁹ H. Fujito, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles* **6**, 379 (1977).

⁵⁰ S. Rossi and E. Duranti, *Tetrahedron Lett.* p. 485 (1973).

⁵¹ K. Eiter and N. Joop, *Naturwissenschaften* **59**, 468 (1972); *Chem. Abstr.* **78**, 16086 (1973).

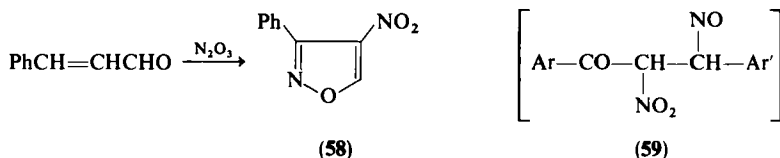
unique in the sense that inorganic nitrite acts as the source of both the nitro group and the two heteroatoms of the nucleus. Probably, intermediate **55** is involved (Scheme 12). Apparently the same type of intermediate is generated



SCHEME 12

by reaction of the type 1 reagent, chloronitroformoxime, with Grignard reagents (**57**; $R = Ph, CH_2O$ -tetrahydropyranyl) from substituted acetylenes. Cyclization leads, as before, to 3-nitro-5-substituted isoxazoles (**56**).^{52,53}

b. 4-Nitroisoxazoles. Some 4-nitroisoxazoles have also been synthesized by procedures in which both the nitro group and the heteroatoms of the nucleus are derived from the same inorganic source. Thus, α,β -unsaturated aromatic aldehydes and ketones give 4-nitroisoxazoles (e.g., **58** from cinnamaldehyde) on treatment with nitrous gases.^{54,55} The intermediate pseudonitrosites (**59**) have been isolated from a series of chalcones which have then been cyclized to 4-nitro-3,5-diaryl isoxazoles.⁵⁵



More complicated reaction sequences have been invoked to explain the formation of eulite (**60**) from citraconic acid and nitric acid [Eq. (18)].⁵⁶

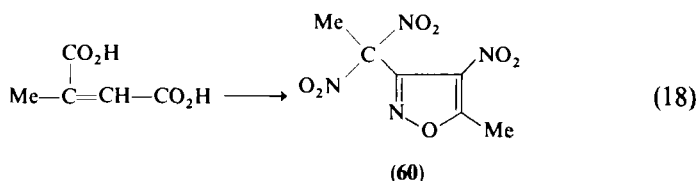
⁵² P. Bravo, *Chim. Ind. (Milan)* **45**, 1239 (1963); *Chem. Abstr.* **60**, 10665 (1964).

⁵³ P. Bravo and G. Gaudiano, *Gazz. Chim. Ital.* **96**, 454 (1966); *Chem. Abstr.* **65**, 2242 (1966).

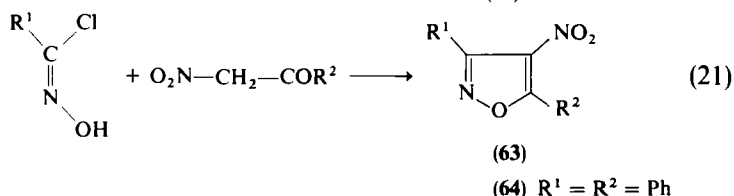
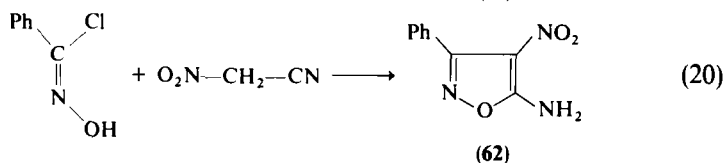
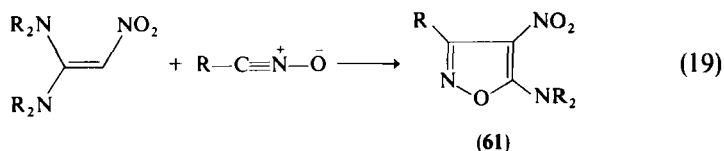
⁵⁴ H. Wieland, *Justus Liebigs Ann. Chem.* **328**, 160, 195, 243, and 245 (1903).

⁵⁵ J.-P. Hauff, J. Tuailon, and R. Perrot, *Helv. Chim. Acta* **61**, 1207 (1978).

⁵⁶ A. Quilico, *Chem. Heterocycl. Compd.* **17**, 29 (1962).



In two examples, type 2 reagents produce 4-nitroisoxazoles. Nitroketeneaminals undergo cycloaddition with nitrile oxides to produce the 4-nitroisoxazoles **61** (10–25%) [Eq. (19)].³⁰ Substrates possessing a methylene group activated on one side by a nitro group and on the other by either a nitrile or a carbonyl, react with hydroxamoyl chlorides in presence of base to produce the 4-nitroisoxazoles **(62)** and **(63)** [Eqs. (20,21)].⁵⁷



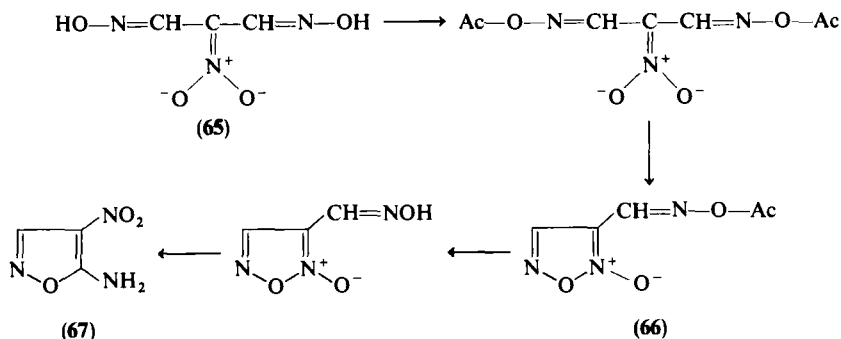
In a typical β -diketone reaction, nitromalonaldehyde reacts with hydroxylamine to produce the parent 4-nitroisoxazole,^{39,58} Similarly, dibenzoylnitromethane yields 3,5-diphenyl-4-nitroisoxazole **64**.⁵⁷

In an interesting sequence of reactions, Grundmann and co-workers have prepared 5-amino-4-nitroisoxazole **(67)** from the sodium salt of nitromalonaldehyde and hydroxylamine.⁵⁹ The initially formed sodium malondialdoxime nitronate **65** is diacetylated and cyclized to the furazan oxide **66**; acid hydrolysis, followed by rearrangement in alkali gives the 5-amino-4-nitroisoxazole (Scheme 13). The same product has also been detected in the decomposition of mercuric fulminate.

⁵⁷ V. Dal Piaz, S. Pinzauti, and P. Lacrimini, *Synthesis* p. 664 (1975).

⁵⁸ A. Quilico, *Chem. Heterocyclic Compd.* **17**, 67 (1962).

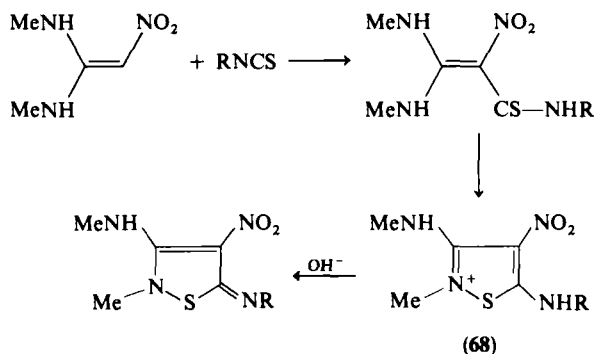
⁵⁹ C. Grundmann, R. K. Bansal, and P. S. Osmanski, *Justus Liebigs Ann. Chem.* **1973**, 898 (1973).



SCHEME 13

3. Nitroisothiazoles

Only one synthesis leads to 2-alkyl-4-nitroisothiazolium salts (**68**) from open-chain precursors. Condensation of nitroketeneaminals with isothiocyanates followed by N—S bond formation using bromine leads to the isothiazoles **68** (20–25%) (Scheme 14).⁶⁰



SCHEME 14

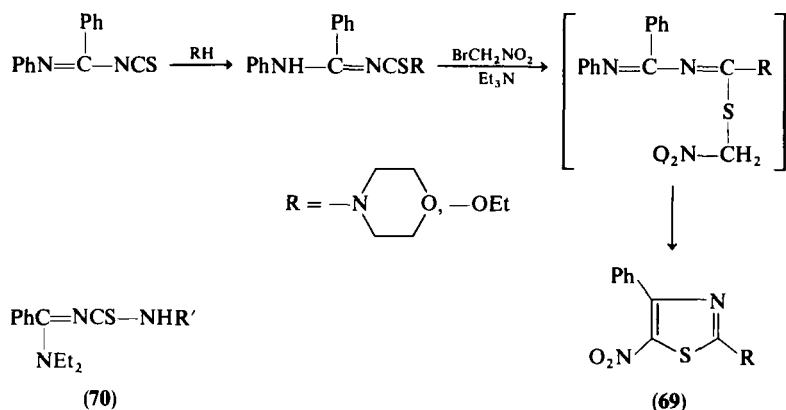
4. Nitrothiazoles

5-Nitrothiazole derivatives have recently become accessible through cyclization procedures.

The versatile bromonitromethane is the nitro-containing synthon in two of these methods. *N*-Phenylbenzimidoyl isothiocyanate reacts with a nucleophile and the adduct is then condensed with bromonitromethane. Cyclization

⁶⁰ S. Rajappa, B. G. Advani, and R. Sreenivasan, *Indian J. Chem.* **15**, 886 (1977).

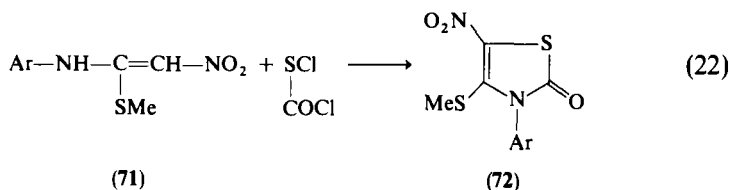
is followed by elimination of aniline, leading to 5-nitrothiazoles (**69**) (Scheme 15).⁶¹



SCHEME 15

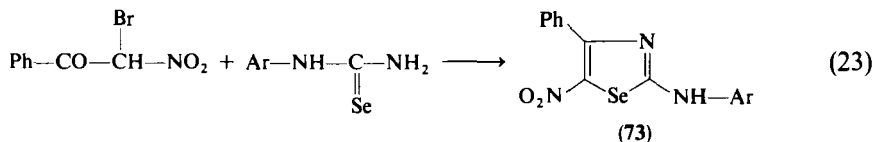
Similarly, the amidine-isothiocyanate adducts (**70**) react with bromonitromethane to give the 5-nitrothiazoles (**69**; R = NHR').⁶²

In a different approach, 1-anilino-1-methylmercapto-2-nitroethylenes (**71**) and chlorothioformylchloride give 5-nitro-3*H*-2-thiazolone derivatives **72** [Eq. (22)].⁶³



5. Nitroselenazoles

Condensation of α -bromo- α -nitroacetophenone with *N*-arylselenoureas has given 5-nitroselenazoles (**73**) [Eq. (23)].⁶⁴



⁶¹ W. Ried and L. Kaiser, *Justus Liebigs Ann. Chem.* **1976**, 395 (1976).

⁶² S. Rajappa and R. Sreenivasan, *Indian J. Chem.* **16**, 749 (1978).

⁶³ H. Schäfer, B. Bartho, and K. Gewald, *J. Prakt. Chem.* **319**, 149 (1977); *Chem. Abstr.* **87**, 68241 (1977).

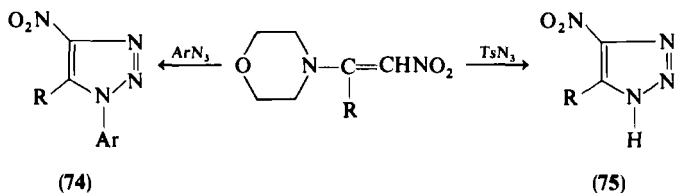
⁶⁴ E. Bulka and P. Oppermann, *Z. Chem.* **17**, 99 (1977).

C. RINGS WITH THREE HETEROATOMS

Nitro-1,2,3-triazoles

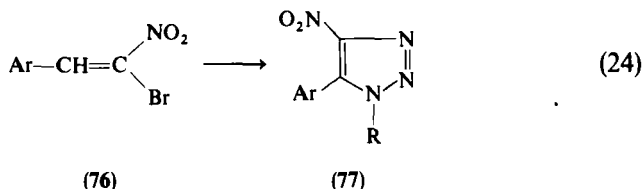
In this group, only the 1,2,3-triazoles seem to have been amenable to synthesis by direct cyclization. Invariably, such syntheses make use of type 2 synthons, leaving only the heteroatoms to be supplied by the complementary reagent.

4-Nitrotriazoles (74) have been prepared by reaction of 1-morpholino-2-nitroethylenes with aryl azides. Tosyl azide also reacts with the nitroenamine, to give the N-unsubstituted triazoles (75) (Scheme 16). In all these reactions, the yields are good (55–75%) when R = H, but much lower (10–30%) when R = Me or Ph.^{38,65,66}



SCHEME 16

Phenyl azide reacts with β -bromo- β -nitrostyrene (76; Ar = Ph) to give 1,5-diphenyl-4-nitro-1,2,3-triazole (77; Ar = R = Ph).⁶⁷ Similarly, bromonitrostyrenes and sodium azide give the nitrotriazoles 77 (R = H) [Eq. (24)].⁶⁸



The addition of phenyl azide to β -nitrostyrene gives 1,5-diphenyl-4-nitro-1,2,3-triazole (77a) in about 20% yield, identical to the product obtained from bromonitrostyrene, described above.⁶⁹ Apparently, cycloaddition occurs in both possible orientations: the intermediate in one case undergoes dehydrogenation to give 77a (Ar = R = Ph), whereas the other adduct loses nitrous acid to produce 1,4-diphenyl-1,2,3-triazole (78) (Scheme 17).

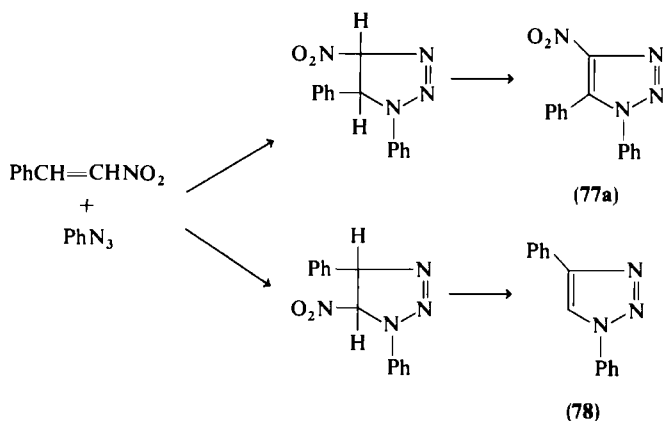
⁶⁵ S. Maiorana, D. Pocar, and P. Dalla Croce, *Tetrahedron Lett.* p. 6043 (1966).

⁶⁶ P. N. Neuman, *J. Heterocycl. Chem.* **8**, 51 (1971).

⁶⁷ G. Rembarz, B. Kirchhoff, and G. Dongowski, *J. Prakt. Chem.* **33**, 199 (1966).

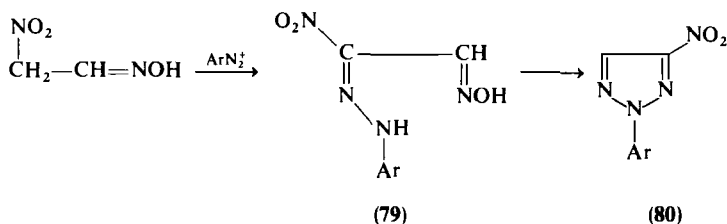
⁶⁸ G. Kh. Khisamutdinov, O. A. Bondarenko, and L. A. Kupriyanova, *Zh. Org. Khim.* **11**, 2445 (1975); *Chem. Abstr.* **84**, 59325 (1976).

⁶⁹ P. D. Callaghan and M. S. Gibson, *Chem. Commun.* p. 918 (1967).



SCHEME 17

Coupling of aromatic diazonium salts with methazonic acid gives the oxime-hydrazones **79**, which can be dehydrated by acid anhydride or acid chloride in alkali to 4-nitro-2H-1,2,3-triazoles (**80**) (Scheme 18).^{70,71}



SCHEME 18

III. Synthesis of Six-Membered Nitro-Heterocycles

A. RINGS WITH ONE HETEROATOM

1. Nitropyridines

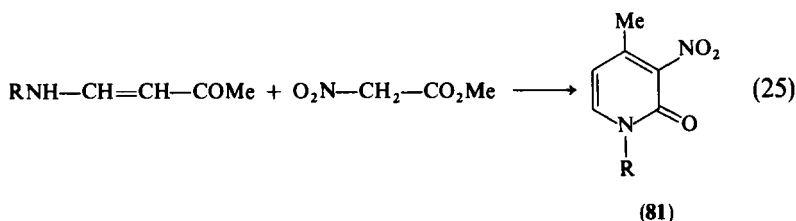
Most of the reported ring syntheses of nitropyridines result in the nitro group occupying position 3 of the pyridine nucleus. Only two reactions have been reported for 4-nitropyridines, of which one leads to a 2,4,6-trinitropyridine.

⁷⁰ H. Lind and H. Kristinsson, *Synthesis* p. 198 (1974).

⁷¹ R. Mohr and M. Zimmermann, German Patent 1,168,437 (1964); *Chem. Abstr.* **61**, 1873 (1964).

a. 3-Nitropyridines. Type 2 and type 3 synthons react with a wide variety of substrates to furnish 3-nitropyridines and their annellated derivatives.

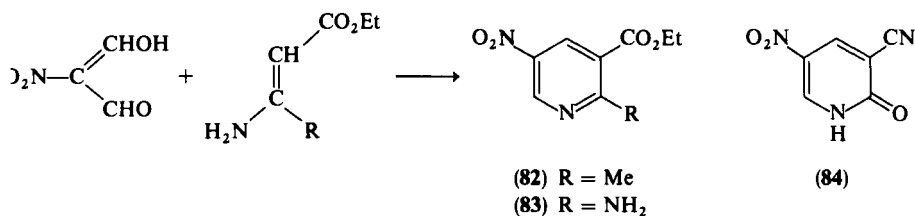
The reaction of enamino-ketones with nitroacetic ester at 60° has been shown to generate the 3-nitropyridones (**81**) [(Eq. (25)).⁷²



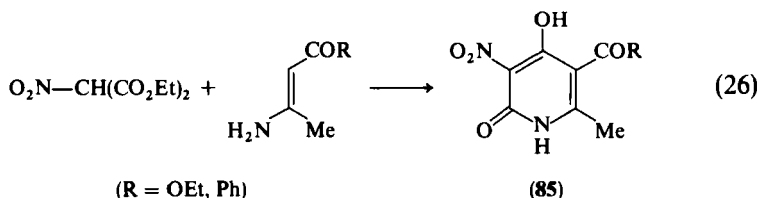
The sodium salt of nitromalonaldehyde reacts with β -aminocrotonic ester to give 2-methyl-5-nitronicotinate (**82**).⁷³

Surprisingly, a preference for the formation of a pyridine rather than a pyrimidine ring is shown in the reaction of sodio-nitromalonaldehyde with ethyl formamidinoacetate; the product is ethyl 2-amino-5-nitronicotinate (**83**).⁷⁴

The condensation of sodio-nitromalonaldehyde with cyanoacetamide in the presence of Triton B gives 3-cyano-5-nitro-2-pyridone (**84**) (93%).⁷⁵



Nitromalonic ester reacts with enamino-ketones and esters to produce the 4-hydroxy-3-nitro-2-pyridones **85** [(Eq. (26)).⁷⁶



⁷² Zh. A. Krasnaya, T. S. Stytsenko, E. P. Prokof'ev, I. P. Yakovlev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.* p. 845 (1974); *Chem. Abstr.* **81**, 49608 (1974).

⁷³ P. E. Fanta, *J. Am. Chem. Soc.* **75**, 737 (1953).

⁷⁴ D. J. Collins, *J. Chem. Soc.* p. 1337 (1963).

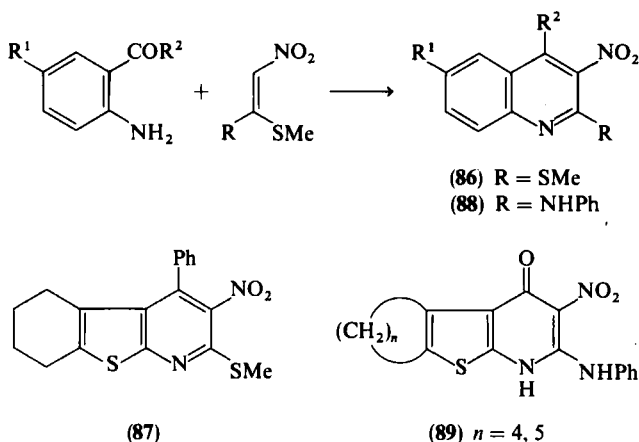
⁷⁵ P. E. Fanta and R. A. Stein, *J. Am. Chem. Soc.* **77**, 1045 (1955).

⁷⁶ A. Dornow and H. von Plessen, *Chem. Ber.* **99**, 244 (1966).

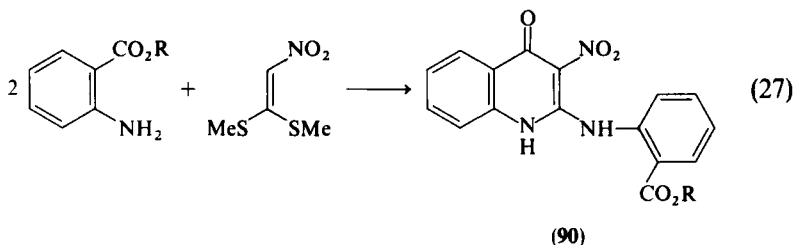
3-Nitroquinoline derivatives have been prepared by cyclization routes from type 2 or type 3 synthons.

1,1-Bis(methylmercapto)-2-nitroethylene reacts with *o*-aminophenyl ketones in presence of acid to give the 3-nitroquinolines **86**.⁷⁷ The condensed thiophene derivative **87** has similarly been prepared.⁷⁷

A variant on this reaction makes use of 1-anilino-1-methylmercapto-2-nitroethylene as the nitro-synthon. This leads to the 2-anilino-3-nitroquinolines **88**.⁷⁸ The reaction is best carried out in acetic acid. The condensed thiophene derivatives **89** have been prepared similarly. The use of anthra-



nilic ester instead of the aminoketones results, with the bis-methylmercaptoethylene, in the formation of the 2-anilino-3-nitro-4-quinolone derivative **90** [Eq. (27)].⁷⁸

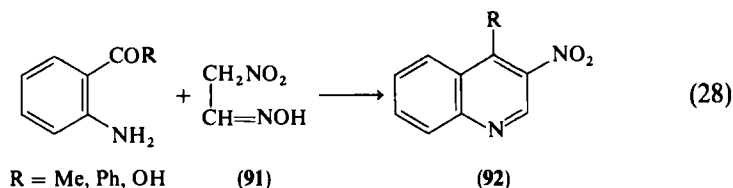


α -Nitrocarbonyl compounds and their derivatives condense with *o*-aminobenzaldehyde or *o*-aminophenyl ketones to provide a wide variety of

⁷⁷ H. Schäfer, B. Bartho, and K. Gewald, *Z. Chem.* **13**, 294 (1973).

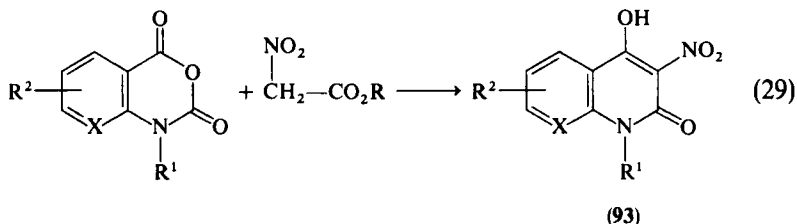
⁷⁸ H. Schäfer, K. Gewald, and M. Seifert, *J. Prakt. Chem.* **318**, 39 (1976).

3-nitroquinolines in good yields.⁷⁹⁻⁸¹ Methazonic acid (**91**) has been used as the nitro-containing synthon in a number of reactions, as in [Eq. (28)].⁸⁰⁻⁸²

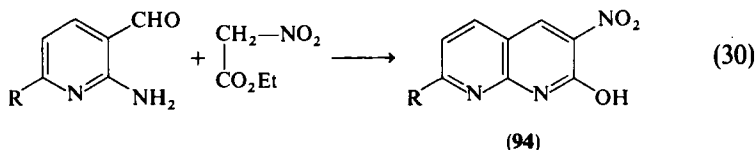


Isatin has been reported to yield 3-nitrocinchoninic acid (**92**; R = CO₂H) with nitromethane in aqueous KOH.⁸³ Although this seems like the use of a type I synthon, it is more appropriate to regard it as another example of a methazonic acid reaction. The reaction of nitroacetone with *o*-aminobenzaldehyde leads to 2-methyl-3-nitroquinoline derivatives.⁸⁴

A series of 4-hydroxy-3-nitro-2-quinolones (**93**; X = CH) has been synthesized from nitroacetic ester and isatoic anhydrides in the presence of sodium hydride [Eq. (29)].⁸⁵ A similar reaction has produced the naphthyridine derivatives **93** (X = N, R² = H).⁸⁶



Similar 2-hydroxy-3-nitro-1,8-naphthyridines (**94**) have been prepared by condensation of 2-aminonicotinaldehydes with nitroacetic ester in the presence of piperidine [Eq. (30)].⁸⁷



⁷⁹ H. E. Baumgarten and J. L. Saylor, *J. Am. Chem. Soc.* **79**, 1502 (1957).

⁸⁰ K. Schofield and R. S. Theobald, *J. Chem. Soc.* p. 395 (1950).

⁸¹ D. W. Ockenden and K. Schofield, *J. Chem. Soc.* p. 3914 (1953).

⁸² G. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Am. Chem. Soc.* **69**, 365 (1947).

⁸³ M. Colonna, *Boll. Sci. Fac. Chim. Ind. Bologna*, p. 89 (1941); *Chem. Abstr.* **37**, 3096 (1943).

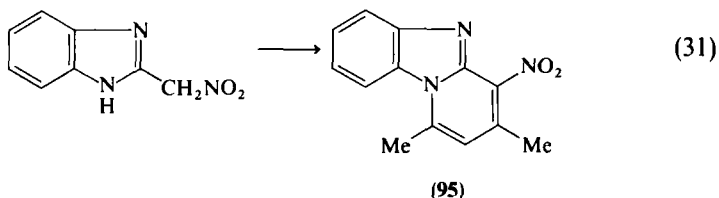
⁸⁴ A. Dornow and W. Sassenberg, *Justus Liebigs Ann. Chem.* **602**, 14 (1957).

⁸⁵ G. E. Hardtmann, Ger. Offen. 2,631,317 (1977); *Chem. Abstr.* **86**, 189742 (1977).

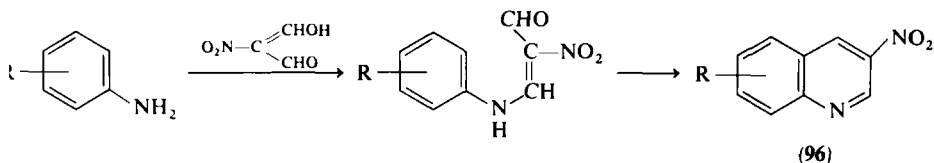
⁸⁶ G. E. Hardtmann, Ger. Offen. 2,635,216 (1977); *Chem. Abstr.* **87**, 23245 (1977).

⁸⁷ E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. C* p. 315 (1966).

A different type of nitro-activated methylene group has been used by Gewald to produce a condensed 3-nitropyridine.⁸⁸ The reaction of 2-nitromethylbenzimidazole with acetylacetone results in the formation of 4-nitro-1,3-dimethylpyrido[1,2-*a*]benzimidazole (**95**) [Eq. (31)].

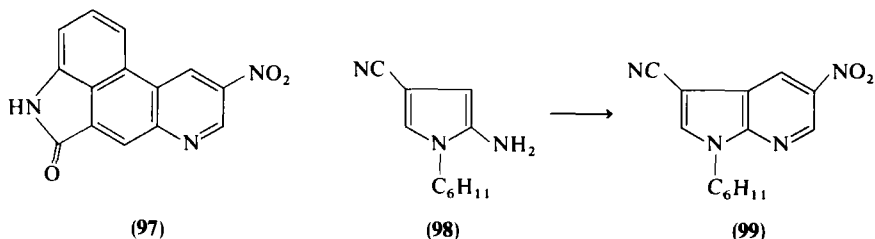


The reaction of anilines with nitromalonaldehyde to form the 3-nitroquinolines (**96**) is carried out in two steps. The cyclization is best catalyzed by the corresponding aniline hydrochloride in acetic acid (Scheme 19).^{89,90} The yields range from 40 to 77%, except in the case of *o*-toluidine, where the yield is very low. The tetracyclic compound **97** has been similarly prepared from 3-aminonaphthostyryl.⁸⁹



SCHEME 19

Nitromalonaldehyde has also been used in the syntheses of nitropyridines condensed to other heterocycles. The success of the reaction depends on the reactivity of the ortho position for cyclization. The 2-amino-4-cyanopyrrole **98** yields the pyrrolo[2,3-*b*]pyridine derivative **99**.⁹¹



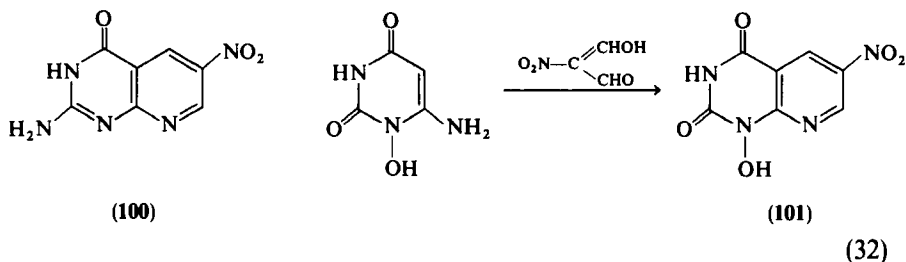
⁸⁸ H. Schäfer and K. Gewald, *Z. Chem.* **16**, 272 (1976).

⁸⁹ F. C. Uhle and W. A. Jacobs, *J. Org. Chem.* **10**, 76 (1945).

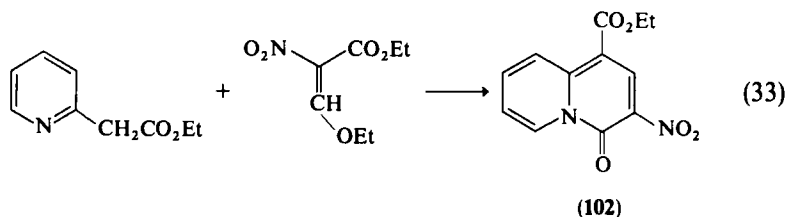
⁹⁰ J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, p. 2024 (1948).

⁹¹ A. Brodrick and D. G. Wibberley, *J. Chem. Soc., Perkin Trans. 1* p. 1910 (1975).

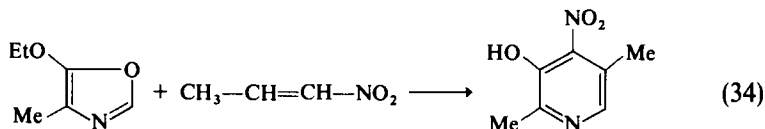
2,4-Diamino-6-hydroxypyrimidine condenses with nitromalonaldehyde in presence of alkali to give 2-amino-4-hydroxy-6-nitropyrido[2,3-*d*]pyrimidine (**100**) (75%).⁹² In a similar reaction 2,4-dioxo-1-hydroxy-6-nitro-1*H*,3*H*-pyrido[2,3-*d*]pyrimidine is formed (**101**) [Eq. (32)].⁹³



Ethyl 2-pyridylacetate has been converted into 1-carbethoxy-3-nitro-4*H*-quinolizin-4-one (**102**) by condensation with ethyl β -ethoxy- α -nitroacrylate [Eq. (33)].⁹⁴



b. 4-Nitro- and 2,4,6-Trinitropyridines. The Diels-Alder reactions of 5-ethoxyoxazoles have been extended (cf. Section II,A,1) to the synthesis of a 4-nitropyridine [Eq. (34)].³



The compound obtained from the potassium salt of 2,2-dinitroethanol and dilute H_2SO_4 ⁹⁵ has been proved to be 2,4,6-trinitropyridine 1-oxide (**103**).^{96,97} It has been shown that 1,1,3,3,5,5-hexanitropentane (**104**; R =

⁹² R. Bernetti, F. Mancini, and C. C. Price, *J. Org. Chem.* **27**, 2863 (1962).

⁹³ T. C. Lee and G. Salemnick, *J. Org. Chem.* **40**, 3608 (1975).

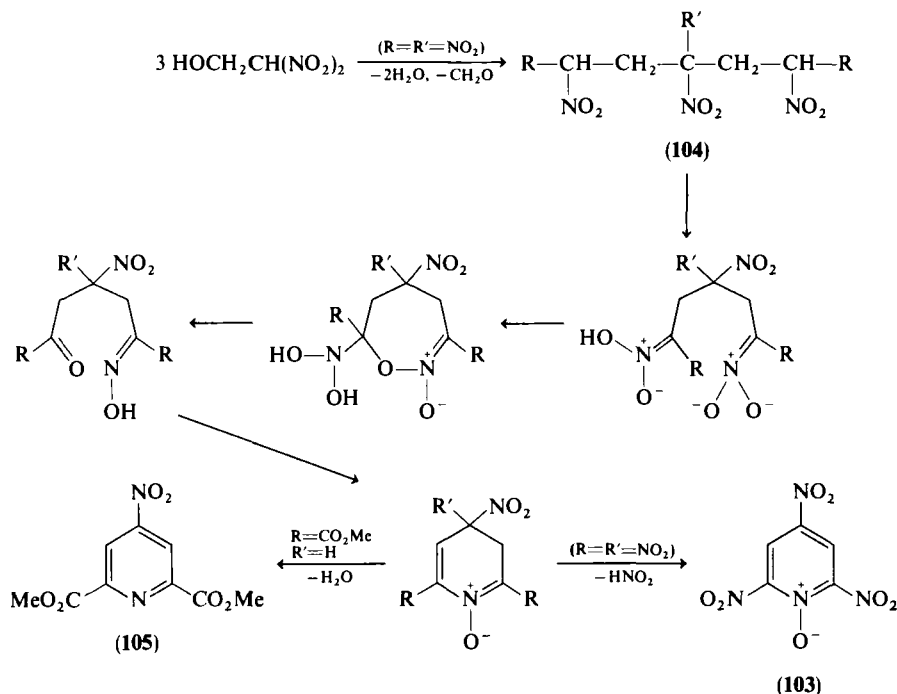
⁹⁴ B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **20**, 1051 (1964).

⁹⁵ P. Duden and G. Ponndorf, *Ber. Dtsch. Chem. Ges.* **38**, 2031 (1905).

⁹⁶ K. D. Gundermann and H. U. Alles, *Angew. Chem., Int. Ed. Engl.* **5**, 846 (1966).

⁹⁷ K. D. Gundermann and H. U. Alles, *Chem. Ber* **102**, 3014 (1969).

$R' = \text{NO}_2$) is an intermediate in this transformation.⁹⁸ This reaction has been exploited to synthesize 4-nitropyridine 2,6-dicarboxylic acid dimethyl ester (**105**) from dimethyl 1,3,5-trinitropentane-1,5-dicarboxylate (**104**; $R = \text{CO}_2\text{Me}$, $R' = \text{H}$).⁹⁹ The suggested course of the reaction is as shown in Scheme 20.



SCHEME 20

2. Nitro γ -Pyrones

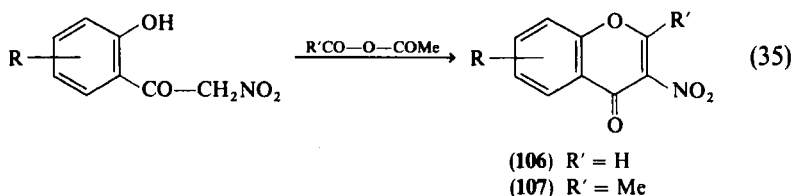
A series of 3-nitrochromones (**106** and **107**) have been prepared from 2'-hydroxy-2-nitroacetophenones.^{100,101} The cyclization is carried out either by means of formic-acetic anhydride and sodium formate or acetic anhydride- H_2SO_4 [Eq. (35)].

⁹⁸ L. I. Bagal, I. V. Tselinskii, and I. N. Shokhor, *Zh. Org. Khim.* **5**, 2016 (1969); *Chem. Abstr.* **72**, 55180 (1970).

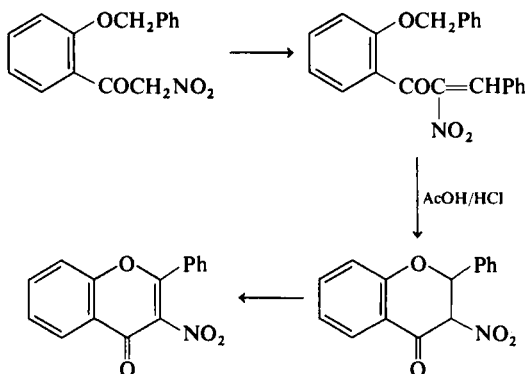
⁹⁹ A. Garmin, D. Redwan, P. Gelbke, D. Kern, and U. Dierkes, *Justus Liebigs Ann. Chem.* **1975**, 1744 (1975).

¹⁰⁰ G. J. P. Becket and G. P. Ellis, *Tetrahedron Lett.* p. 719 (1976).

¹⁰¹ K. V. Rao and V. Sundaramurthy, *Indian J. Chem.* **15**, 236 (1977).



3-Nitroflavone has been obtained by conversion of *o*-benzyloxy-2-nitroacetophenone to the chalcone, debenzoylation and cyclization to the 3-nitroflavanone,¹⁰² and aromatization by bromination-dehydrobromination (Scheme 21).¹⁰³



SCHEME 21

B. RINGS WITH TWO HETEROATOMS

1. Nitropyridazines

There has been one report each on the synthesis of 3-nitro and 4-nitropyridazine derivatives by direct ring closure.

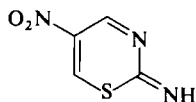
a. 3-Nitropyridazines. Malonic ester reacts with 1-dimethylamino-2-nitroethylene in the presence of potassium ethoxide to give the nitronate salt **108**. This can be coupled with aromatic diazonium salts and the resulting hydrazone cyclized thermally, or by alumina, to the 3-nitro-1-arylpyridazinones **109** (Scheme 22).¹⁰⁴

¹⁰² G. I. Samokhvalov, M. K. Shakhova, M. I. Budagyants, A. Ya. Veinberg, L. V. Luk'yanova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.* **31**, 1147 (1961), *Chem. Abstr.* **55**, 24731 (1961).

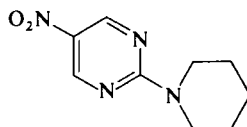
¹⁰³ M. Michalska, *Chem. Ind. (London)* p. 628 (1966).

¹⁰⁴ T. Severin, B. Brück, and P. Adhikary, *Chem. Ber.* **99**, 3097 (1966).

Thiourea has also been reacted with nitromalonaldehyde. According to Hale and Brill, the condensation of sodio-nitromalonaldehyde with thiourea in presence of piperidine gives the thiazine **119**.¹¹⁵ However, this observation could not be confirmed; subsequent work has given only 5-nitro-2-piperidinopyrimidine (**120**) under these conditions in 15% yield.¹¹⁶ These workers

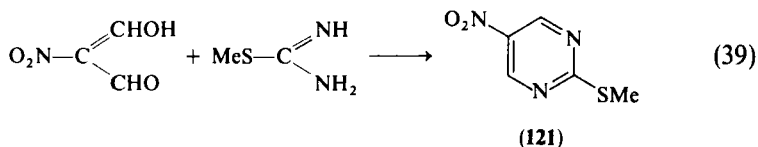


(119)

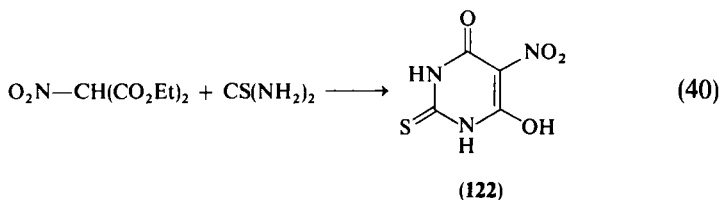


(120)

have obtained 2-methylthio-5-nitropyrimidine (**121**) in 26% yield from sodio-nitromalonaldehyde and *S*-methylisothiuronium sulfate in presence of 1-ethylpiperidine [Eq. (39)]. Use of piperidine as the base in this reaction leads to the 2-piperidino derivative **120**.



Nitromalonic ester reacts with thiourea to yield 2-thio-5-nitrobarbituric acid (**122**) [Eq. (40)].¹¹⁷



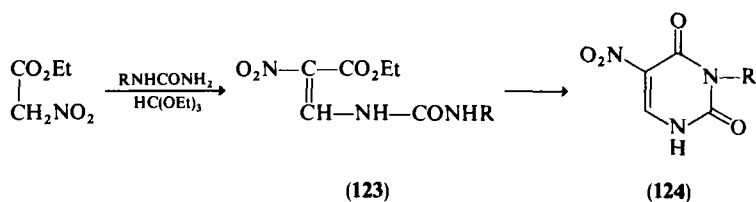
Ethyl nitroacetate reacts with urea or its *N*-mono-substituted derivatives in the presence of triethyl orthoformate to produce the ureidomethylene derivatives **123**. These can be easily cyclized by sodium alkoxide to 5-nitro-uracil derivatives (**124**)¹¹⁸ (Scheme 24). Use of *N,N'*-dimethylurea leads

¹¹⁵ W. J. Hale and H. C. Brill, *J. Am. Chem. Soc.* **34**, 295 (1912).

¹¹⁶ M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.* p. 1218 (1951).

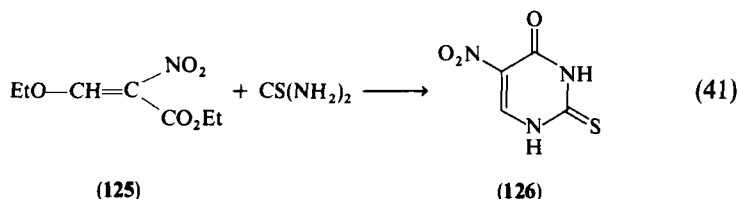
¹¹⁷ R. Nutiu, I. Sebe, and M. Nutiu, *Rev. Roum. Chim.* **19**, 679 (1974); *Chem. Abstr.* **81**, 49646 (1974).

¹¹⁸ M. Prystas and J. Gut, *Collect. Czech. Chem. Commun.* **28**, 2501 (1963).

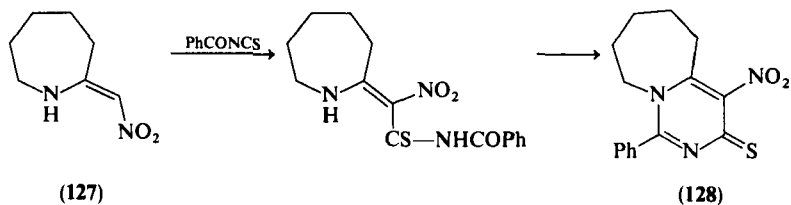


SCHEME 24

directly to 1,3-dimethyl-5-nitouracil. Condensation of ethyl ethoxymethylenenitroacetate (**125**) with thiourea in the presence of sodium ethoxide gives 2-thio-5-nitouracil (**126**) [Eq. (41)] but in very low yield.¹¹⁸



Several condensed 5-nitropyrimidine derivatives have also been prepared from appropriate nitro-containing precursors. 2-Nitromethylene hexahydroazepine (**127**) forms an adduct with benzoyl isothiocyanate which, during recrystallization from acetic acid, cyclizes to the pyrimido[3,4-*a*]azepine **128** (Scheme 25).¹¹⁹ This seems to be the only example of the use of a type 2 synthon for the synthesis of a 5-nitropyrimidine.

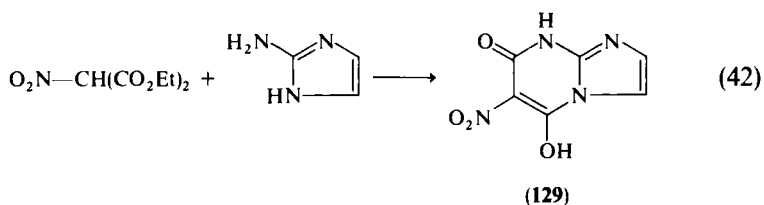


SCHEME 25

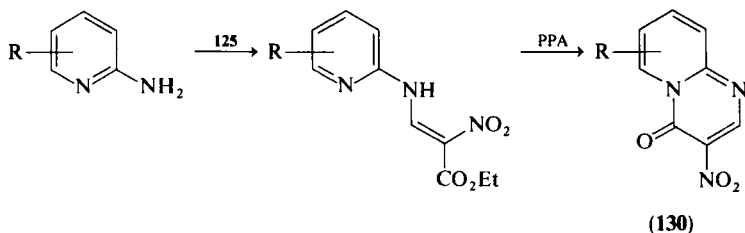
2-Aminoimidazole, being a cyclic guanidine, condenses with nitromalonic ester to give the imidazo[1,2-*a*]pyrimidine **129** [Eq. (42)].¹²⁰

¹¹⁹ S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summerville, and R. Hoffmann, *Indian J. Chem.* **15**, 297 (1977).

¹²⁰ D. E. O'Brien, R. K. Robins, and L. N. Simon, U.S. Patent, 3,907,799 (1975); *Chem. Abstr.* **84**, 4998 (1976).



The synthesis of 3-nitropyrido[1,2-*a*]pyrimidines (**130**) has been reported recently.¹²¹ The product obtained from the condensation of ethyl ethoxymethylenenitroacetate and 2-aminopyridines has been cyclized with the aid of polyphosphoric acid (Scheme 26). The yields in the cyclization are in the region of 65–75%, provided the temperature is kept in the narrow range of 85°–95°.



SCHEME 26

¹²¹ O. S. Wolfbeis, *Chem. Ber.* **110**, 2480 (1977).

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Isoxazole Chemistry Since 1963

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* This review was written during the tenure of D. J. W. as an honorary Visiting Research Fellow at the University of Salford.

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I. Introduction

When recent advances in the chemistry of isoxazoles were reviewed by Kochetkov and Sokolov¹ in this Series in 1963 (and by Quilico² in 1962), the main features of isoxazole chemistry had been established. Since then some important new discoveries have been made, but probably the most significant advances have concerned the exploitation of the known features of their chemistry in synthesis. Particularly noteworthy developments include the further application of the cycloaddition of nitrile oxides in the synthesis of isoxazoles (Section II,C and D), the use of isoxazolium salts in peptide synthesis (Section III,B,2), syntheses involving the products of reductive cleavage of isoxazoles as intermediates (Section III,D and E) and annelation reactions via deprotonation of alkylisoxazoles (Section III,E).

The scope of this review is similar to that of the earlier one.¹ Thus, isoxazolines, isoxazolidines (see Takeuchi and Furusaki³), and benzisoxazoles (see Wünsch and Boulton⁴) are not included, except for comparison or where such compounds are intermediates in or products of reactions discussed.

Papers published up to the end of 1977 have been systematically covered (though a great deal of selection was necessary), and some 1978 references are included.

II. Synthesis of the Isoxazole Ring

A. INTRODUCTION

The synthetic routes to isoxazoles may be classified according to the number of isoxazole ring atoms in each component synthon (e.g., 3 + 2),

¹ N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocycl. Chem.* **2**, 365 (1963).

² A. Quilico, in "Five- and Six-Membered Compounds with Oxygen and Nitrogen" (R. H. Wiley, ed.), p. 1. Wiley (Interscience), New York, 1962.

³ Y. Takeuchi and F. Furusaki, *Adv. Heterocycl. Chem.* **21**, 207 (1977).

⁴ K. H. Wünsch and A. J. Boulton, *Adv. Heterocycl. Chem.* **8**, 277 (1969).

the type of ring atom in each component (e.g., C—C—C + N—O), and the chemical class to which each component belongs (e.g., 1,3-dicarbonyl compound + hydroxylamine). The previous review¹ dealt exclusively with (3 + 2) routes, and these continue to be of prime importance, especially the 1,3-dipolar cycloaddition reactions of nitrile oxides with C=C and C≡C dipolarophiles, on which the present review concentrates. Some (4 + 1) and further (5 + 0) reactions have also been reported, which provide some new regiospecific routes to isoxazole systems. The (5 + 0) reactions involve cyclization of synthons containing all five ring atoms, usually in the sequence C—C—C—N—O. The long-established (3 + 1 + 1) route⁵ involving condensation reactions of nitro compounds in the presence of base appears now to be little used, while as far as we are aware (2 + 2 + 1) routes have not yet been reported. Isoxazoles have also been prepared by several ring-transformation reactions.

B. SYNTHETIC ROUTES EXCLUDING THOSE INVOLVING CHLOROXIMES AND NITRILE OXIDES

1. (3 + 2) Routes

a. (CCC + NO) Routes. Initially the CCC unit was more often than not a 1,3-dicarbonyl system, usually a 1,3-diketone or -ketoaldehyde. Since these were believed to react as their enol tautomers, it was logical to extend the scope of the synthesis by using β -substituted vinyl ketones. α,β -Acetylenic ketones are also used. The 3-ketoaldehydes are often more conveniently used as derivatives such as acetals. For unsymmetrical CCC units the possibility of forming two not easily separable 3,5-disubstituted products is a disadvantage. However, the dependence of the isomer ratio on the substituents, and sometimes on reaction conditions (see later discussion), allows the reaction in many cases to be regiospecific, or nearly so. In this context, a study of the direction of enolization of unsymmetrical 1,3-diketones has been made by mass spectrometry.⁶

If one of the atoms of the CCC unit is part of an ester grouping, an isoxazolone will usually result; if part of a cyano group, an aminoisoxazole will be formed. Substitution on the central atom of the CCC unit leads to 4-substitution in the resulting isoxazole. The NO unit is always hydroxylamine

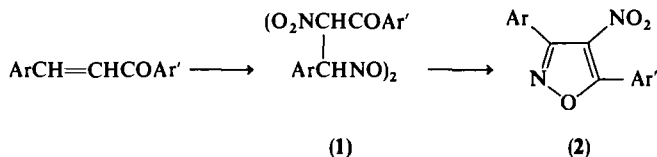
⁵ W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.* **59**, 410 (1891).

⁶ K. S. R. K. M. Rao and P. L. K. M. Rao, *Proc. Indian Acad. Sci., Sect. A* **81**, 262 (1975).

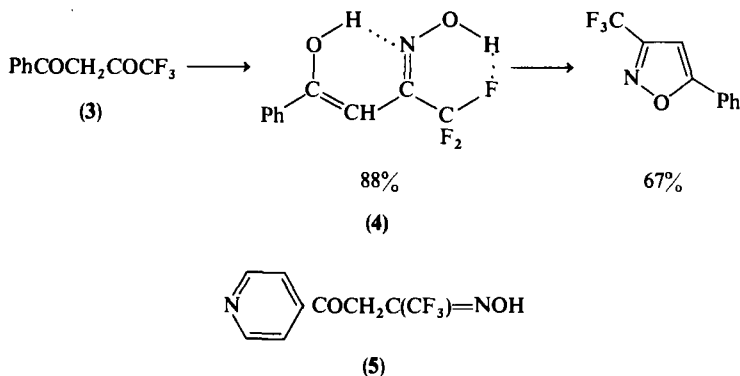
or one of its N-substituted derivatives; the latter lead to N-substituted isoxazolines.

Reactions in which the CCC unit is part of a ring, with attack by hydroxylamine leading to a labile acyclic intermediate which recycles to form an isoxazole, are classified as ring transformations (Section II,B,4).

Only the general principles of these types of reactions are given here. The literature is replete with references to such reactions, but in most of them the established procedures previously reviewed are employed.^{1,2} A few variations are worthy of mention. Dinitrogen trioxide has very recently been used in place of hydroxylamine in reaction with α,β -unsaturated ketones.⁷ The resulting pseudonitrosites (1), obtained in 17–42% yields, were thermally cyclized to 3,5-diaryl-4-nitroisoxazoles (2).



Oximation of the β -diketone (3) gave the H-bonded enol form of the monooxime (4).⁸ Its Z-configuration and resistance to further attack by hydroxylamine were attributed to chelation, which is also regarded as responsible for the forced regiospecificity. Cyclization was effected by heating with acetyl chloride, a procedure also claimed for the cyclization of the oxime (5).⁹

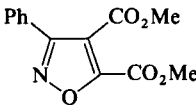
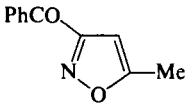
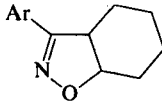
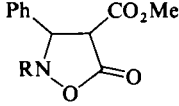
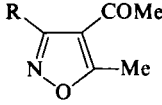
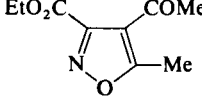


⁷ J. -P. Hauff, J. Tuailon, and R. Perrot, *Helv. Chim. Acta* **61**, 1207 (1978).

⁸ J. B. Carr, H. G. Durham, and D. K. Hass, *J. Med. Chem.* **20**, 934 (1977).

⁹ V. J. Bauer and S. R. Safir, British Patent 1,178,604 (1970); *Chem. Abstr.* **72**, 79017 (1970).

TABLE I
 (CNO + CC) ROUTES TO ISOXAZOLES^a

CNO Component	CC Component	Product	Reference
$\text{PhCH}=\text{N}^+(\text{OAc})\text{O}^-$	$\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$		12
$\text{PhCOCH}=\text{N}^+(\text{O}^-)_2$	$\text{CH}_2=\text{C}(\text{Me})\text{OCOMe}$		13
$\text{ArC}(\text{Br})=\text{N}^+(\text{O}^-)_2$	cyclo- C_6H_{10}		14
$\text{PhCH}=\text{N}^+(\text{R})\text{O}^-$	$\text{CH}_2(\text{CO}_2\text{Me})_2$		15
$\text{RCH}=\text{NOH}$	$\text{MeCOCH}_2\text{COMe}$		16
$\text{HON}=\text{C}(\text{OEt})\text{CH}_2\text{Cl}$	$\text{MeCOCH}_2\text{COCH}_2\text{Me}$		17

^a Isoxazolines are included where potentially capable of conversion into isoxazoles (see Section II,D).

2. (4 + 1) Routes

Relatively few of these reactions have been reported, although they can provide convenient routes to isoxazoles in which the substituents are unequivocally located. Examples are given in Eqs. (1)–(6).^{18–23}

¹⁸ M. Dines and M. L. Scheinbaum, *Tetrahedron Lett.* p. 4817 (1969).

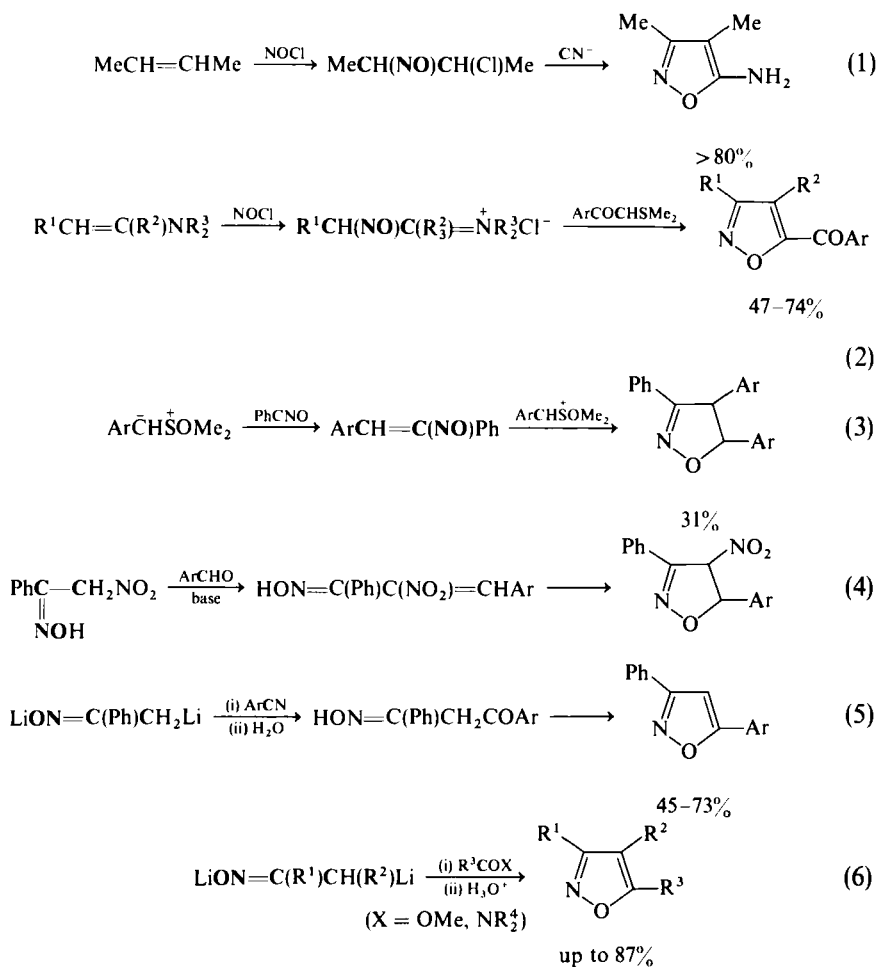
¹⁹ P. Bravo and C. Ticozzi, *Gazz. Chim. Ital.* **105**, 91 (1975).

²⁰ R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. I* p. 1196 (1977).

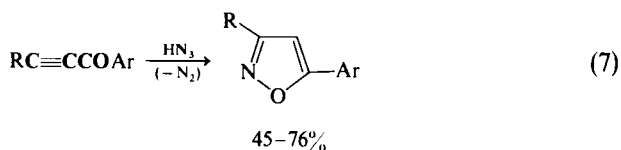
²¹ G. K. Khistamutdinov, L. A. Demina, N. T. Severina, and E. V. Vandakurova, *Zh. Org. Khim.* **13**, 230 (1977).

²² C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Heterocycl. Chem.* **9**, 183 (1972).

²³ M. Perkins, C. F. Beam, M. C. D. Dyer, and C. R. Hauser, *Org. Synth.* **55**, 39 (1976); G. N. Barber and R. A. Olofson, *J. Org. Chem.* **43**, 3015 (1978).



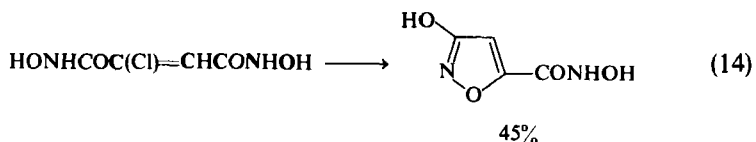
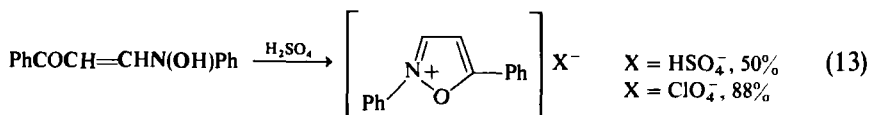
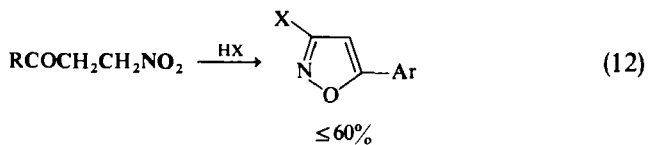
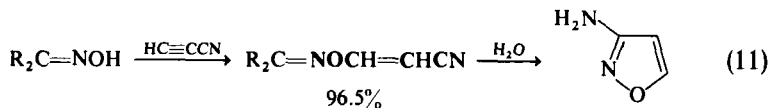
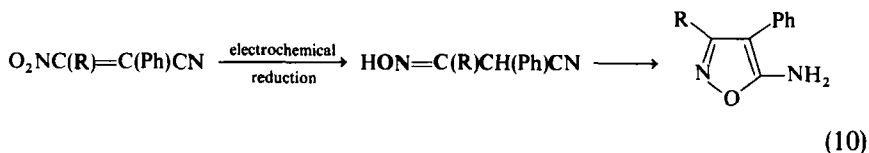
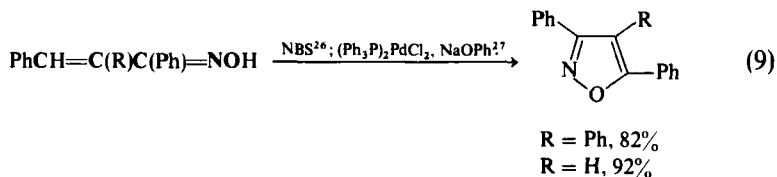
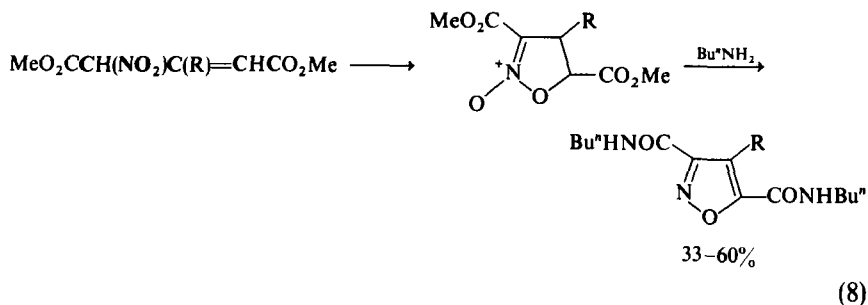
The above examples involve (CCNO + C) combinations. One example of a (CCCO + N) synthesis is shown in Eq. (7).²⁴



²⁴ U. Türck and H. Behringer, *Chem. Ber.* **98**, 3020 (1965).

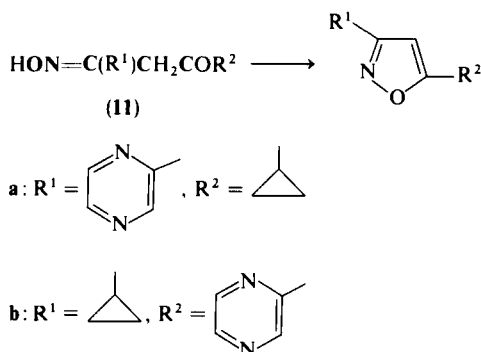
3. (5 + 0) Routes

All reactions leading to isoxazoles (except true concerted cycloadditions of nitrile oxides and possibly some photochemical reactions) must involve, at some stage, cyclization of a system which contains all five atoms of the

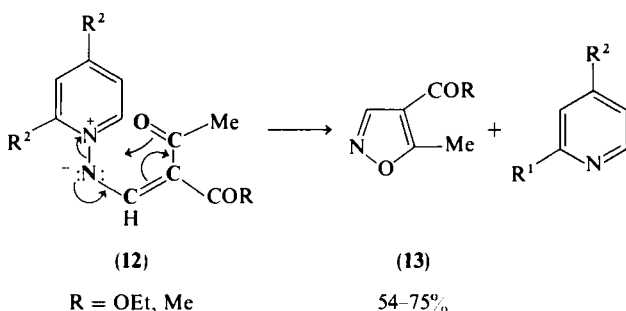


isoxazole ring. In some cases the acyclic intermediates are short-lived and unisolable, in others they are stable and capable of isolation. Equations (8)–(14) illustrate reactions for which the acyclic precursor is either the starting material or an isolable intermediate.^{1,8,25–31} As with (4 + 1) routes, the substituents are unambiguously located.

The reaction conditions employed for cyclization may be important. For example, in sulfuric acid both the oximes **11** cyclized in about 15% yield, whereas in ethanolic hydrogen chloride only **11a** did so, in 94% yield. The difference was attributed to the influence of the nitrogen of the pyrazine ring.³²



All of the preceding reactions involve CCCNO synthons, except Eq. (11) which has NOCCC. Examples of OCCCN cyclizations are also rare.



²⁵ S. Zen and E. Kaji, *Chem. Pharm. Bull.* **22**, 477 (1974).

²⁶ J. F. Hansen and S. A. Strong, *J. Heterocycl. Chem.* **14**, 1289 (1977).

²⁷ K. Maeda, T. Hikosawa, S. Murahashi, and I. Moritani, *Tetrahedron Lett.* p. 5075 (1973).

²⁸ C. Bellec, R. Colau, S. Deswarte, J. C. Doré, and C. Viel, *C. R. Hebd. Seances Acad. Sci., Ser. C* **281**, 885 (1975).

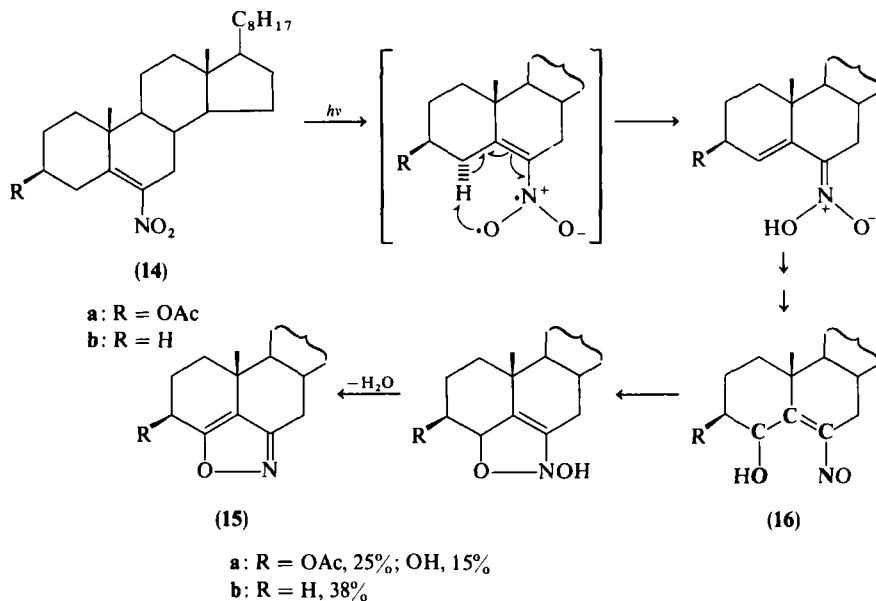
²⁹ K. Morita, N. Hashimoto, and K. Matsumura, *Ger. Offen.* 1,814,116 (1969); *Chem. Abstr.* **71**, 124415 (1969).

³⁰ R. B. Woodward and D. J. Woodman, *J. Org. Chem.* **31**, 2039 (1966).

³¹ J. W. Hines and C. H. Stammer, *J. Med. Chem.* **20**, 965 (1977).

³² L. S. Crawley and W. J. Fanshawe, *J. Heterocycl. Chem.* **14**, 531 (1977).

Intermediate **12**, on heating in benzene, gives the isoxazole **13**, whereas related compounds give, for example, pyrazolo[1,5-*a*] pyridines.³³ Irradiation of the 6-nitrocholest-5-enes **14** in acetic acid at reflux gave the steroidal isoxazoles **15**. It was proposed that the isoxazoles were formed via the labile intermediate **16**, which was formed by hydrogen abstraction as shown in Scheme 1. The possible importance of this method for functionalizing a nonactivated carbon atom was pointed out.³⁴ We are unaware of examples involving CCNOC and CNOCC synthons.



SCHEME 1

4. Ring Transformations Leading to Isoxazoles

Very many syntheses of isoxazoles from other heterocyclic compounds have been reported. The subject of ring transformations of heterocycles has been well reviewed³⁵⁻³⁷; and since many of the reactions are covered by the categories already discussed (the starting heterocycle serving merely as precursor of the appropriate intermediate), only a brief summary, with

³³ Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1* p. 2580 (1973).

³⁴ J. T. Pinhey, E. Rizzardo, and G. C. Smith, *Aust. J. Chem.* **31**, 113 (1978).

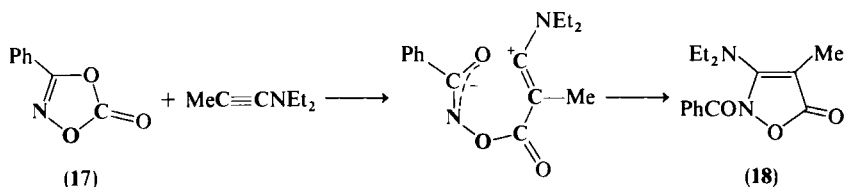
³⁵ H. C. van der Plas, "Ring Transformations of Heterocycles," Vols. 1 and 2. Academic Press, New York, 1973.

³⁶ O. Buchardt, ed., "Photochemistry of Heterocyclic Compounds." Wiley, New York, 1976.

³⁷ Specialist Periodical Reports, "Aromatic and Heteroaromatic Chemistry," Vols. 1-5. Chem. Soc., London, 1973-1977.

leading references, is given here. The interconversion of oxazoles, acylazirines, and isoxazoles is discussed in Section III,C.

Many of the reported transformations are of more theoretical than practical interest. However, ring contraction of condensed 4-pyrones continues to play a useful role in the synthesis of steroidal isoxazoles.^{38,39} The stepwise, polar addition of an electron-rich, multiply bonded component to an easily cleaved cyclic electron acceptor has been proposed as a strategy for the synthesis of a variety of heterocyclic systems.⁴⁰ The formation of the isoxazolone **18** from the 1,3,5-dioxazolidone **17** and diethylaminopropyne exemplifies the principle. This reaction is also interesting in that compound **17** represents a cyclic NOC synthon.



Other ring transformations giving isoxazoles (or isoxazolines capable of conversion into isoxazoles) are as follows: ring expansion of oxirans⁴¹ and oxetanones⁴²; ring contraction of pyrimidines, pyrimidinium salts, pyrimidine *N*-oxides,⁴³ pyrylium salts,⁴⁴ ketonylidene-pyrans,⁴⁵ chromones, thiochromones, chromylium salts,⁴⁶⁻⁵¹ and oxazinones;⁵² photoisomeriza-

³⁸ G. D. Beresford, R. C. Cambie, and K. P. Mathai, *Aust. J. Chem.* **26**, 1763 (1973).

³⁹ P. Crabbé, L. A. Maldonado, and I. Sanchez, *Tetrahedron* **27**, 711 (1971).

⁴⁰ R. Gompper and J. Stetter, *Tetrahedron Lett.* p. 233 (1973).

⁴¹ H. J. Roth and M. Schwarz, *Arch. Pharm. (Weinheim, Ger.)* **294**, 769 (1961).

⁴² M. Fujimoto and M. Sakai, *Chem. Pharm. Bull.* **13**, 248 (1965).

⁴³ R. Peereboom and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **93**, 277, 284 (1974); H. C. van der Plas, M. C. Vollering, H. Jongejan, and B. Zuurdeeg, *ibid.* p. 225; R. Peereboom, H. C. van der Plas, and A. Koudijs, *ibid.* p. 58; J. Clark and M. Curphey, *J. Chem. Soc., Chem. Commun.* p. 184 (1974).

⁴⁴ C. L. Pedersen, O. Buchardt, S. Larsen, and K. J. Watson, *Tetrahedron Lett.* p. 2195 (1973); G. N. Dorofeenko, A. V. Koblik, B. A. Tertov, and T. I. Polyakova, *Khim. Geterotsikl. Soedin.* p. 1016 (1973); *Chem. Abstr.* **79**, 137021 (1973).

⁴⁵ P. Caramella and A. Querci, *Chim. Ind. (Milan)* **53**, 556 (1971); P. Crabbé, J. Haro, C. Rius, and E. Santos, *J. Heterocycl. Chem.* **9**, 1189 (1972).

⁴⁶ R. Beugelmans and C. Morin, *J. Org. Chem.* **42**, 1356 (1977).

⁴⁷ W. Basinski and Z. Jerzmanowska, *Rocz. Chem.* **48**, 989 (1974); **51**, 2283 (1977).

⁴⁸ A. Nohara, *Tetrahedron Lett.* p. 1187 (1974).

⁴⁹ M. A. -F. Elkashef, F. M. C. Abdel-Megeid, K. -E. M. Mokht, and M. F. Elbarnashawi, *Indian J. Chem.* **11**, 860 (1973).

⁵⁰ G. N. Dorofeenko, V. V. Thachenko, and V. V. Mezheritskii, *Khim. Geterotsikl. Soedin.* 465 (1975).

⁵¹ C. L. Pedersen and O. Buchardt, *Acta Chem. Scand., Ser. B* **29**, 285 (1975).

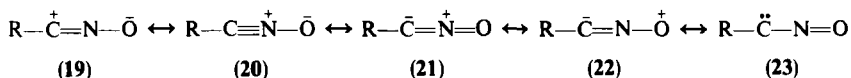
⁵² Y. Yamamoto and Y. Azuma, *Heterocycles* **9**, 185 (1978).

tion of pyridazinedioxides,⁵³ other transformations of pyrrolenines,⁵⁴ furans,⁵⁵ dithioles,⁵⁶ oxaphosphazoles,⁵⁷ and benzotriazepines.⁵⁸

C. NITRILE OXIDES IN THE SYNTHESIS OF ISOXAZOLES

1. Preparation and Properties of Nitrile Oxides

The chemistry of nitrile oxides has been well reviewed (see, for example, Grundmann *et al.*⁵⁹⁻⁶¹), and only those features which are pertinent to the synthesis of isoxazoles are summarized here. The electronic structure may be represented as a hybrid of the canonical forms 19-23. The formula 20 is commonly used, but formula 19 embodies their 1,3-dipolar character, and formula 23 their nitrosocarbonoid nature.



Nitrile oxides display three types of reactivity (apart from isomerization and deoxygenation): 1,3-cycloaddition, 1,3-addition, and dimerization to furoxans. The first can give isoxazolines and isoxazoles directly. The second can give isoxazolines and isoxazoles indirectly. The third (which may be regarded as a carbenoid reaction,⁶² but see also Lo Vecchio *et al.*⁶³) is an undesirable side reaction as far as the synthesis of isoxazoles is concerned. Thus, although many methods for generating nitrile oxides are available, and in some cases they may be isolated and used, methods capable of generating them in the presence of the substrate are preferred.

a. Preparation from Chloroximes. The most widely used precursors for nitrile oxides are the chloroximes (hydroximoyl chlorides) (24), which are

⁵³ H. Arai, A. Ohsawa, K. Saiki, H. Igeta, A. Tsuji, T. Akimoto, and Y. Iitaka, *J. Chem. Soc., Chem. Commun.* p. 856 (1977).

⁵⁴ T. Ajello and C. Petronici, *Gazz. Chim. Ital.* **72**, 333 (1942).

⁵⁵ H. Wamhoff and F. Korte, *Chem. Ber.* **99**, 2962 (1966); H. Meister and G. Peitscher, *Justus Liebigs. Ann. Chem.* **1974**, 1908 (1974).

⁵⁶ F. Boberg and W. von Gentzkow, *Justus Liebigs Ann. Chem.* **1973**, 256 (1973).

⁵⁷ T. Sasaki, T. Yoshioka, and Y. Suzuki, *J. Soc. Org. Synth. Chem., Tokyo Jpn.* **28**, 1054 (1970).

⁵⁸ M. Bianchi, A. Butti, and S. Rossi, *Tetrahedron* **30**, 2765 (1974).

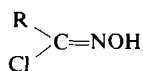
⁵⁹ C. Grundmann and P. Grünanger, "The Nitrile Oxides." Springer-Verlag, Berlin and New York, 1971.

⁶⁰ C. Grundmann, *Synthesis* p. 344 (1970); *Fortschr. Chem. Forsch.* **7**, 62 (1966).

⁶¹ A. Quilico, *Experientia* **26**, 1169 (1970); *Chim. Ind. (Milan)* **53**, 157 (1971).

⁶² R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **2**, 565 (1963); but see G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc. B* p. 588 (1970).

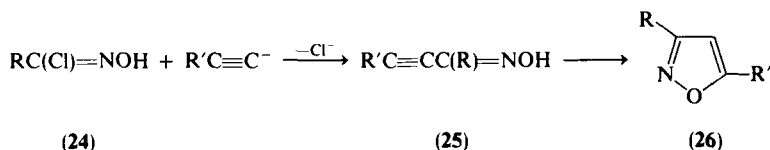
⁶³ G. Lo Vecchio, F. Foti, G. Grassi, and F. Risitano, *Tetrahedron Lett.* p. 2119 (1977).



(24)

conveniently prepared from aldoximes and chlorine or nitrosyl chloride.^{64,65} The chloroximes are readily converted into nitrile oxides by treatment with base, commonly triethylamine. In cases where the nitrile oxide dimerizes rapidly and the substrate is base-sensitive, the dehydrohalogenation can be carried out at temperatures as low as -20° .⁶⁶ In the absence of base most chloroximes are stable at room temperature, and even at higher temperatures the equilibrium between chloroxime, nitrile oxide, and hydrogen chloride favors chloroxime.⁶⁷ However, thermal dissociation in an inert solvent in which hydrogen chloride has low solubility (e.g., boiling toluene) can be used to generate the nitrile oxide in the presence of substrate.⁶⁸⁻⁷⁰

It should be noted that it is in many cases conceivable that isoxazoles and isoxazolines are formed from chloroximes without the intermediacy of a nitrile oxide. This route could occur if the substrate acted as a nucleophile to give an intermediate, such as the alkynyloxime (25) from an acetylide, which can cyclize to the isoxazole (26). In this case, by trapping with nonnucleophilic alkenes, the reaction has been shown to involve a nitrile oxide.^{60,71} However, experiments on reactions of chloroximes with other nucleophiles suggest that a nitrile oxide is not invariably involved.^{72,73}



(24)

(25)

(26)

A suggestion has been made that in some cases cycloaddition of an alkyne and loss of hydrogen chloride may be effectively synchronous.⁶⁸

⁶⁴ R. H. Wiley and B. J. Wakefield, *J. Org. Chem.* **25**, 546 (1960); Y. H. Chiang, *ibid.* **36**, 2146 (1971).

⁶⁵ R. Lenaers and F. Eloy, *Helv. Chim. Acta* **46**, 1067 (1963); G. Zinner and H. Günther, *Angew. Chem., Int. Ed. Engl.* **3**, 383 (1964).

⁶⁶ G. Casnati and A. Ricca, *Tetrahedron Lett.* p. 327 (1967).

⁶⁷ J. Armand, P. Souchay, and F. Valentini, *Bull. Soc. Chim. Fr.* p. 4585 (1968).

⁶⁸ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **40**, 2604 and 2608 (1967).

⁶⁹ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **41**, 2206 (1968).

⁷⁰ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **42**, 258 (1969); T. Sasaki, T. Yoshioka, and Y. Suzuki, *ibid.* p. 3335.

⁷¹ G. F. Bettinetti and C. Fraschini, *Gazz. Chim. Ital.* **100**, 403 (1970).

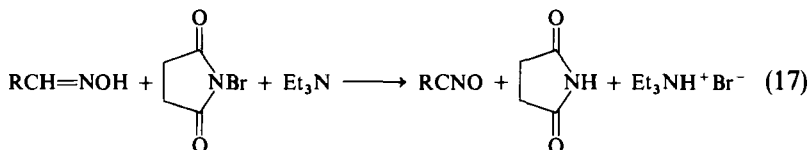
⁷² E. Jedlovská, J. Kovac, A. Piklerová, and P. Zalupsky, *Collect. Czech. Chem. Commun.* **41**, 3085 (1976).

⁷³ T. Sasaki, T. Yoshioka, and Y. Suzuki, *J. Synth. Org. Chem., Jpn.* **27**, 877 (1969).

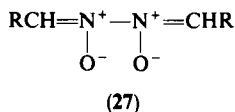
b. Preparation from Aldoximes. Several reagents have been used to oxidize aldoximes to nitrile oxides.^{59,60} Lead(IV) acetate [Eq. (15)] is effective at temperatures as low as -78° .



Alkaline hypobromite [Eq. (16)] is experimentally convenient; both this reagent and *N*-bromosuccinimide in the presence of triethylamine [Eq. (17)] may involve a bromoxime intermediate.



Nitrogen dioxide at 0° gives a dimeric intermediate, possibly **27**, which on heating gives nitrile oxide and aldoxime.⁷⁴



c. Other Methods of Preparation. Some analogs of chloroximes that have been used as precursors for nitrile oxides are nitrooximes (from nitroalkanes and nitrous acid),⁵⁹ α -ketodiazooximes $\text{RCOC(N}_2\text{)=NOH}$ (for α -ketonitrile oxides),⁷⁵ and iodoformaldoxime ICH=NOH (for formonitrile oxide HCNO).⁶⁰ The dehydration of primary nitroalkanes with phenyl isocyanate has also been used to prepare nitrile oxides.⁵⁹

Nitrile oxides have been detected, often by trapping as isoxazoles, as intermediates in the cleavage of a number of heterocycles including furoxans,^{76,77} furazans,^{78,79} and 1,3,2,4-dioxathiazole-2-oxides.⁸⁰

⁷⁴ C. Grundmann and G. F. Kite, *Synthesis* p. 156 (1973).

⁷⁵ H. Dahn, B. Favre, and J.-P. Leresche, *Helv. Chim. Acta* **56**, 457 (1973).

⁷⁶ J. F. Barnes, R. M. Paton, P. L. Ashcroft, R. Bradbury, J. Crosby, C. J. Joyce, D. R. Holmes, and J. A. Milner, *J. Chem. Soc., Chem. Commun.* p. 113 (1978); J. A. Chapman, J. Crosby, C. A. Cummings, and R. A. C. Rennie, *ibid.* p. 240 (1976); M. Sakamoto, M. Shibano, and Y. Tomimatsu, *Yakugaku Zasshi* **93**, 1643 (1973); *Chem. Abstr.* **80**, 59887 (1974).

⁷⁷ M. Altaf-ur-Rahman, A. J. Boulton, and D. Middleton, *Tetrahedron Lett.* p. 3469 (1972); J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton and R. C. Brown, *J. Chem. Soc., Perkin Trans. I* p. 1587 (1972).

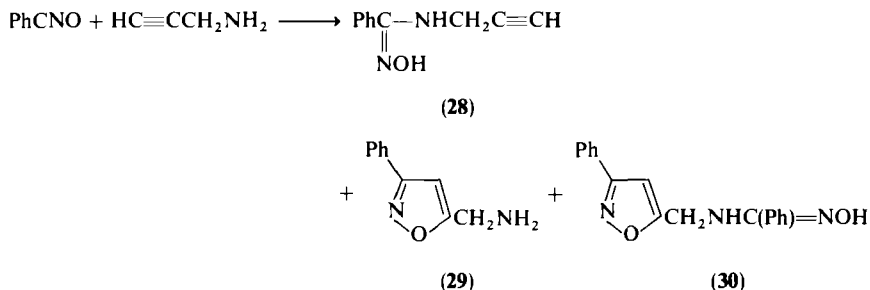
⁷⁸ Y. Ivari, S. Esfandiari, A. J. Mostashari, and P. W. W. Hunter, *J. Org. Chem.* **40**, 2880 (1975).

⁷⁹ A. J. Boulton and S. S. Mathur, *J. Org. Chem.* **38**, 1054 (1973).

⁸⁰ J. E. Franz and H. K. Pearl, *J. Org. Chem.* **41**, 1296 (1976).

2. Reactions of Nitrile Oxides with Alkynes

Of the systems showing 1,3-dipolar reactivity, the nitrile oxide is possibly the longest known and is one of the most reactive.^{81,82} Such reactivity shows itself in the great variety of both acyclic- (via 1,3-addition) and heterocyclic structures (via 1,3-cycloaddition) that can be synthesized from them.⁵⁹ In the reactions of nitrile oxides with terminal alkynes, both modes of reaction occur, leading to alkynyloximes (**25**) and isoxazoles (**26**). The former readily cyclize to the latter but have been detected or isolated in some cases.^{83,84} In some substituted alkynes 1,3-addition of a substituent may compete with cycloaddition of the triple bond. For example, the reaction between benzonitrile oxide and 3-aminopropyne gives a mixture of the 1,3-adduct (**28**) (ca. 40%), the 1,3-cycloadduct (**29**) (ca. 5%), and the product of both modes of reaction (**30**) (ca. 15%).⁸⁵ Competition can also occur



between carbon-carbon triple bonds and other multiple bonds; the former are more reactive than carbon-nitrogen triple bonds but less reactive than carbon-carbon and carbon-nitrogen double bonds.⁵⁹

The mechanism of 1,3-cycloaddition of nitrile oxides has been a subject of sometimes bitter controversy. While these reactions displayed the regioselectivity and stereoselectivity appropriate to concerted pericyclic mechanisms,⁶² it was suggested that the results were equally in accord with a diradical mechanism.⁸⁶ However, no direct evidence for a diradical intermediate has been produced, and the balance of the theoretical argument now favors the

⁸¹ E. Howard, *Philos. Trans. R. Soc. London* **90**, 204 (1800).

⁸² W. Fliege and R. Huisgen, *Justus Leibigs Ann. Chem.* **1973**, 2038 (1973).

⁸³ S. Morrocchi, A. Ricca, A. Zanarotti, G. Bianchi, R. Gandolfi, and P. Grünanger, *Tetrahedron Lett.* p. 3329 (1969); A. Battaglia, A. Dondoni, and A. Mangini, *J. Chem. Soc. B* p. 554 (1971); P. Beltrame, P. Sartirana, and C. Vintani, *ibid.* p. 814 (1971); A. Dondoni and G. Barbaro, *J. Chem. Soc., Perkin Trans. 2* p. 159 (1974).

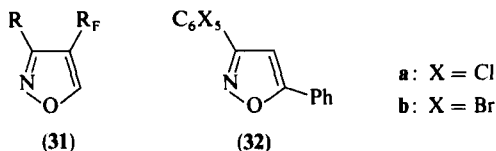
⁸⁴ B. Iddon, H. Suschitzky, A. W. Thompson, B. J. Wakefield, and D. J. Wright, *J. Chem. Res (S)* p. 174; (*M*) p. 2038 (1978).

⁸⁵ P. Caramella and P. Vita Finzi, *Chim. Ind. (Milan)* **48**, 963 (1966).

⁸⁶ R. A. Firestone, *J. Org. Chem.* **37**, 2181 (1972).

concerted mechanism (Huisgen,⁸⁷ and references therein). A number of theoretical studies based on a concerted mechanism have been published.⁸⁸

Regardless of the mechanism, three clear generalizations concerning the reactions can be made. First, in cycloadditions to monosubstituted (alkyl/aryl) alkynes only the 5-substituted isoxazole is obtained. Only in the case of perfluoroalkylalkynes has any significant amount of the 4-substituted isomer (31) been observed.⁸⁹ Second, the reaction is hindered by bulky substituents on the alkyne. Finally, the reaction is not appreciably hindered by bulky substituents on the nitrile oxide, even when they are so large as to inhibit dimerization almost completely.⁵⁹ Competition for phenylethyne between pentachloro- and pentabromobenzonitrile oxide gave approximately equimolar amounts of the two adducts (32).⁹⁰



The potential of the reaction of nitrile oxides with alkynes was already recognized at the time of the earlier review.¹ The realization of that potential was apparent 7 years later in the comprehensive account by Grundmann and Grünanger.⁵⁹ In Table II we list a selection of the syntheses reported in the period 1970–1978, illustrating new applications of the method and some of the generalizations discussed.^{59, 71, 84, 89, 91–100}

⁸⁷ R. Huisgen, *J. Org. Chem.* **41**, 403 (1976).

⁸⁸ P. Beltrame, P. L. Beltrame, and P. Caramella, *Gazz. Chim. Ital.* **106**, 531 (1976); G. Bianchi, C. De Micheli, and R. Gandolfi, *J. Chem. Soc., Perkin Trans. 1* p. 1518 (1976); D. Poppinger, *J. Am. Chem. Soc.* **97**, 7486 (1975); J. Bastide and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.* p. 1037 (1974); J. Bastide, O. Henri-Rousseau, and E. Stephen, *C. R. Hebd. Seances Acad. Sci., Ser. C* **278**, 195 (1974); K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973).

⁸⁹ U. Gallucci, M. Le Blanc, and U. G. Riess, *J. Chem. Res. (S)* p. 198; (*M*) p. 2529 (1978).

⁹⁰ D. J. Wright, Ph.D. Thesis, Salford University (1977).

⁹¹ B. J. Wakefield and D. J. Wright, *J. Chem. Soc. C* p. 1165 (1970).

⁹² G. A. Shvekhgeimer and O. A. Volskaya, *Khim. Geterotsikl. Soedin.* p. 180 (1975).

⁹³ L. B. Sokolov, L. K. Vagina, V. N. Chistokletov, and A. A. Petrov, *Zh. Org. Khim.* **2**, 615 (1966).

⁹⁴ Z. Hamlet, M. Rampersad, and D. J. Shearing, *Tetrahedron Lett.* p. 2101 (1970).

⁹⁵ D. P. Deltsova, E. S. Ananyan, and N. P. Gambaryan, *Izv. Akad. Nauk. SSSR, Ser. Khim.* p. 362 (1971).

⁹⁶ P. Bravo, A. Ricca, G. Ticozzi, and O. V. De Pava, *Gazz. Chim. Ital.* **106**, 743 (1976).

⁹⁷ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **44**, 803 (1971).

⁹⁸ H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.* **40**, 2143 (1975).

⁹⁹ T. Sasaki, and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **41**, 2212 (1968).

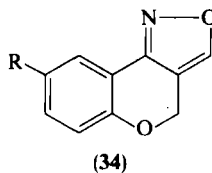
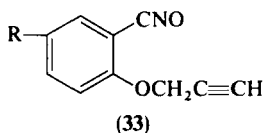
¹⁰⁰ R. Fusco, L. Garanti, and G. Zecchi, *Chim. Ind. (Milan)* **57**, 16 (1975).

TABLE II
ISOXAZOLES FROM NITRILE OXIDES AND ALKYNES

Type of alkyne	Product(s) isolated	Reference
Alk-1-yne	5-Substituted isoxazoles	84, 91, 92
Perfluoroalkylalk-1-yne	4- And 5-perfluoroalkylisoxazoles	89
Diyne, enynes	Bis(isoxazoles), 5-alkynyl- and 5-alkenylisoxazoles, 5-alkynylisoxazolines.	59, 93
Sodio- and magnesio-alkynes ^a	5-Substituted isoxazoles	71, 94
1-Alkoxy- and 1-dialkyl-amino-alkynes	5-Alkoxyisoxazoles, 5-dialkylaminoisoxazoles	95
1-Acylalkynes	Usually 4-acyl-5-substituted isoxazoles	96, 97
2-Ynoic esters	Isoxazole-5- and/or 4-carboxylates	98
Propargyl derivatives	5-Substituted isoxazoles ^b	96
Cyanoethyne	4- And 5-cyanoisoxazoles	99

^a Direct reaction with chloroxime; see p. 159.

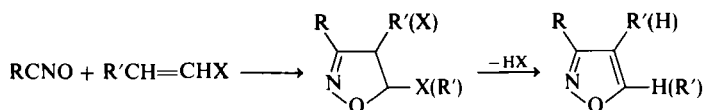
^b In an intramolecular cycloaddition, the propargyl ether **33** is constrained to give the 4-substituted isoxazole (**34**).¹⁰⁰



3. Reactions of Nitrile Oxides with Alkenes

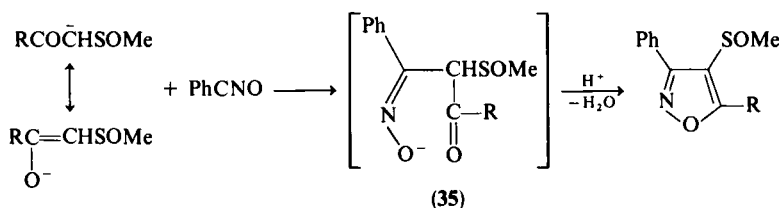
As noted, alkynes are in general less reactive toward nitrile oxides than alkenes. They are also usually less readily available. It would therefore be useful to be able to carry out reactions between nitrile oxides and alkenes, and convert the resulting isoxazoline into the desired isoxazole. This goal can be achieved in two ways: by using an alkene bearing a substituent which leads to ready elimination from the product; and by dehydrogenating the product in a separate reaction (see Section II,D).

The general characteristics of the reactions of nitrile oxides with alkenes resemble those of the reactions with alkynes.⁵⁹ The main differences are (i) that there is no evidence for a two-stage mechanism (1,3-addition followed by cyclization) and (ii) that although they are generally regioselective, they are not always markedly so. A further characteristic is that they are stereospecific with respect to the alkene, whose geometry is preserved in the product.



SCHEME 2

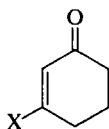
The general route for the reactions leading to isoxazoles is shown in Scheme 2. A variation, using enolate ions as the substrate, is illustrated by the example shown in Scheme 3.¹⁰¹ As indicated, the isoxazole could be formed by cyclodehydration of an open-chain intermediate such as **35**.



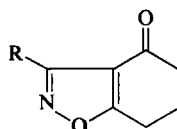
SCHEME 3

TABLE III
ISOXAZOLES FROM NITRILE OXIDES AND C=C DIPOLAROPHILES

Dipolarophile	Product(s) isolated	Reference
Allenic esters	4- and/or 5-substituted isoxazoles	102
Ketene mercaptals, aminsals	5-Alkylthio-, 5-alkylaminoisoxazoles	103
Vinyl halides	Isoxazole	104
1,1-Dichloroethene	5-Chloroisoxazole	105
β -Substituted vinyl halides	5-Substituted isoxazoles	106, 107
Substituted cyclohexenones (36)	4-Oxo-4,5,6,7-tetrahydroindoxazenes	107



(36)



X = OH, OMe, OAc, Cl, NH₂, NR₂

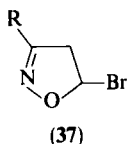
Phosphonium allylides	4-Substituted isoxazoles	108
Azidovinyl ketones	Acyloisoxazoles	109
1,3-Diketones	4-Acyl-5-substituted isoxazoles	110
Nitromethyl ketones	4-Nitro-5-substituted isoxazoles	111
β -Cyanoenamines	4-Cyanoisoxazoles	112

¹⁰¹ P. Bravo and P. P. Ponti, *J. Heterocycl. Chem.* **10**, 669 (1973).

Some recent examples¹⁰²⁻¹¹² illustrating the scope of both types of reaction are listed in Table III.

D. DEHYDROGENATION OF ISOXAZOLINES TO ISOXAZOLES

The lability of the isoxazole ring precludes the use of drastic conventional reagents for aromatizing dihydroisoxazoles. However, two satisfactory methods are now available. The first involves bromination by *N*-bromo-succinimide to give an intermediate (**37** or the 4-bromo isomer) which is readily dehydrobrominated without being isolated, either spontaneously or on treatment with weak base.¹¹³



Very recently it has been reported that 4,5-dihydroisoxazoles are dehydrogenated essentially quantitatively by treatment with active γ -manganese dioxide, the water formed in the reaction being removed by azeotropic distillation.¹¹⁴

III. Reactions of Isoxazoles

A. REACTIONS WITH ELECTROPHILES

1. Electrophilic Substitution

It was well established by previous work that electrophilic substitution in the isoxazole ring proceeds readily and occurs in the 4-position.¹ Quantita-

¹⁰² P. Battioni, L. Vo-Quang, J. -C. Raymond, and Y. Vo-Quang, *C. R. Hebd. Seances Acad. Sci., Ser. C* **271**, 1468 (1970).

¹⁰³ S. Rajappa, B. G. Advani, and R. Sreenivasan, *Synthesis* p. 656 (1974).

¹⁰⁴ R. G. Micetich, *Can. J. Chem.* **48**, 3753 (1970).

¹⁰⁵ R. G. Micetich, *Org. Prep. Proc. Int.* **2**, 225 (1970).

¹⁰⁶ R. Verbruggen and H. G. Viehe, *Chimia* **29**, 350 (1975).

¹⁰⁷ A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and A. G. Pozdeyev, *Synthesis* p. 43 (1978), and references therein.

¹⁰⁸ P. Dalla Croce and D. Pocar, *J. Chem. Soc., Perkin Trans. 1* p. 619 (1976).

¹⁰⁹ G. L. 'Abbé and G. Mathys, *J. Org. Chem.* **39**, 1221 (1974).

¹¹⁰ F. Arena, F. Manna, M. L. Stein, and L. Parente, *Farmaco, Ed. Sci.* **30**, 380 (1975).

¹¹¹ V. Dal Piaz, S. Pinzauti, and P. Lacrimini, *Synthesis* p. 664 (1975).

¹¹² A. Corsaro, U. Chiacchio, and G. Purrello, *J. Chem. Soc., Perkin Trans. 1* p. 2154 (1977).

¹¹³ G. Bianchi and P. Grünanger, *Tetrahedron* **21**, 817 (1965).

¹¹⁴ A. Barco, S. Benetti, G. P. Pollini, and P. G. Baraldi, *Synthesis* p. 837 (1977).

TABLE IV
REACTIVITIES TOWARD
ACID-CATALYZED DEUTERIODEPROTONATION^a

Position	log (partial rate factor) ^b			
	2	3	4	5
Isoxazole	—	—	4.3	—
Isothiazole	—	—	3.6	—
Furan	8.2	ca. 4.5	ca. 4.5	8.2
Thiophene	8.6	5.0	5.0	8.6
1-Methylimidazole	—	5.6	9.8	5.6

^a See Clementi *et al.*¹¹⁵

^b Relative to one position of benzene = 1.

tive information on the reactivity of isoxazole was obtained by studies on acid-catalyzed deuteriodeprotonation.¹¹⁵ In 30% D₂SO₄, exchange was observed only in the 4-position and only in the unprotonated substrate. The reactivity of isoxazole is compared with those of benzene and some five-membered heterocycles in Table IV. Some activation is provided by methyl groups in the 3- and 5-positions, and despite the increased basicity of the compounds (see Section III,A,2) both hydrogen exchange and nitration occur on the free base.¹¹⁶

Electrophilic substitution of arylisoxazoles has been the subject of conflicting reports, but the currently accepted position may be summarized as follows. Both 3- and 4-phenylisoxazoles are nitrated and brominated almost exclusively at the para position of the phenyl group.¹¹⁷ 5-Phenylisoxazole, however, undergoes nitration in the 4-position and in both meta and para positions of the phenyl group¹¹⁸ (cf. Kochetkov and Sokolov¹). The presence of deactivated 3- or 5-aryl groups (e.g., *p*-nitrophenyl) can result in nitration largely at the 4-position.^{117,119} 3-Methyl-5-phenylisoxazole undergoes nitration as the conjugate acid at the para position of the phenyl group, whereas 5-methyl-3-phenylisoxazole is nitrated both as the conjugate acid

¹¹⁵ S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *J. Chem. Soc., Perkin Trans. 2* p. 399 (1974).

¹¹⁶ A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. B* p.2365 (1971).

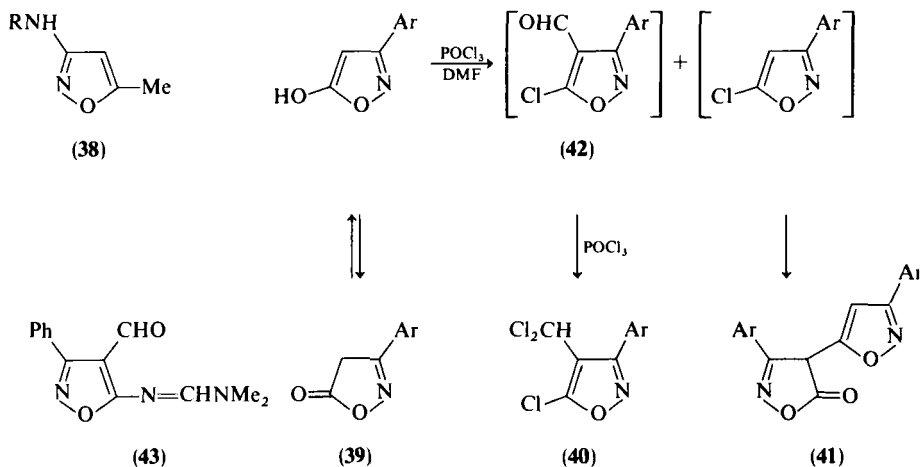
¹¹⁷ V. Bertini, A. De Munno, V. Dell'Amico, and P. Pino, *Gazz. Chim. Ital.* **97**, 1604 (1967); A. De Munno, V. Bertini, and F. Lucchesini, *Chim. Ind. (Milan)* **58**, 880 (1976).

¹¹⁸ S. D. Sokolov and I. M. Yudintseva, *Zh. Org. Khim.* **4**, 2057 (1968).

¹¹⁹ S. D. Sokolov, I. M. Yudintseva, P. V. Petrovskii, and V. G. Kalyuzhnaya, *Zh. Org. Khim.* **7**, 1979 (1971).

at the meta position and as the free base at the para position of the phenyl group.¹²⁰

In many cases electrophilic substitution in isoxazoles bearing activating groups proceeds predictably. For example, 3-amino-5-methylisoxazole and related compounds (**38**; R = H, CO₂Me, SO₂Ar) are brominated and iodinated in the 4-position under appropriate conditions.¹²¹ On the other hand, Vilsmeier–Haack formylation is not straightforward. For example, the isoxazol-5(4*H*)-ones **39** gave compounds **40** and/or **41** depending on the conditions; it was suggested that they were formed from the formyl derivative (**42**) as shown in Scheme 4.¹²² Vilsmeier–Haack formylation of 5-amino-3-phenylisoxazole gives the aldehyde **43**, which is a useful intermediate for the synthesis of isoxazolopyridines.¹²³



SCHEME 4

2. Protonation and Quaternization

Isoxazoles are only weakly basic. Isoxazole has a pK_a of -2.97 at 25° , and the values for the 3-, 5-, and 3,5-dimethyl derivatives are -1.62 , -2.01 ,

¹²⁰ A. R. Katritzky, M. Konya, H. O. Tarhan, and A. G. Burton, *J. Chem. Soc., Perkin Trans. 2* p. 1627 (1975).

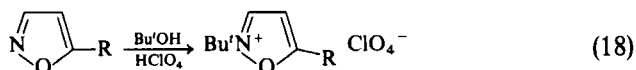
¹²¹ N. Saito, T. Kurihara, K. Yamanaka, S. Tsuruta, and S. Yasuda, *Yakugaku Zasshi* **88**, 1289 (1968); S. Sumimoto, T. Makikado, and H. Kano, Japanese Patent 70/38,527; *Chem. Abstr.* **74**, 87945 (1971).

¹²² R. K. M. R. Kallury and P. S. U. Devi, *Tetrahedron Lett.* p. 3655 (1977).

¹²³ H. Yamanaka, T. Sakamoto, and A. Shiozawa, *Heterocycles* **7**, 51 (1977).

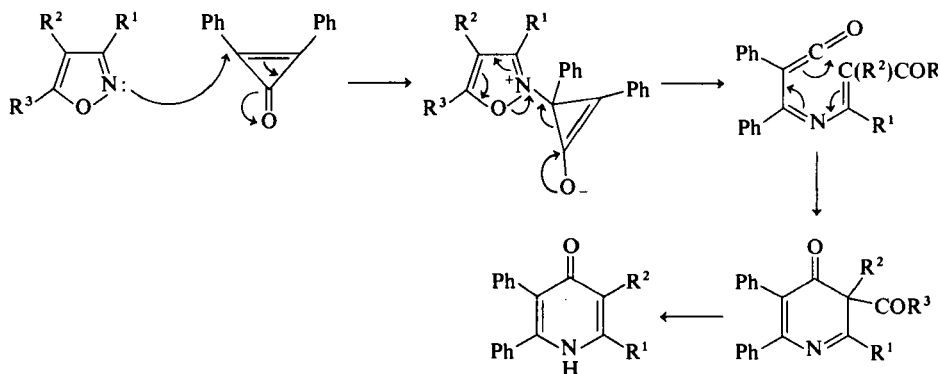
and -1.61 , respectively; a 4-nitro group reduces the pK_a of 3,5-dimethylisoxazole to -6.43 .^{115,116} For five 4-substituted 3,5-diphenylisoxazoles the pK_a values showed a good correlation with the Hammett σ_m constants for the substituents.¹²⁴

Isoxazolium salts can be prepared by appropriate general methods, although the low basicity of the isoxazoles and their sensitivity to nucleophilic attack may necessitate special care. The explosive nature of isoxazolium perchlorates must be noted.¹²⁵ The preparation of isoxazolium salts containing bulky N-substituents can be very difficult, and the particular utility of such compounds in synthesis (see Section III,B,2) has prompted the development of new methods for preparing them. A noteworthy route involving the reaction of the isoxazole with a carbenium ion, formed from a suitable alcohol, is exemplified in Eq. (18).^{30,126}



A pathway of this type may be involved in the acid-catalyzed reaction of isoxazoles with mesityl oxide.¹²⁷

Isoxazoles apparently behave as nucleophiles in their reactions with diphenylcyclopropanone, leading to pyridones.¹²⁸ The mechanism of this transformation is not established, but the route proposed (Scheme 5) is



SCHEME 5

¹²⁴ S. D. Sokolov and L. B. Tikhomirova, *Khim. Geterotsikl. Soedin.* p. 1029 (1976).

¹²⁵ B. D. Wilson and D. M. Burness, *J. Org. Chem.* **31**, 1565 (1966).

¹²⁶ D. J. Woodman, *J. Org. Chem.* **33**, 2397 (1968).

¹²⁷ C. H. Eugster, L. Lechner, and E. Jenny, *Helv. Chim. Acta* **46**, 543 (1963).

¹²⁸ R. Grigg, R. Hayes, J. L. Jackson, and T. J. King, *J. Chem. Soc., Chem. Commun.* p. 349 (1973).

plausible. In a case where the 4-position was unsubstituted ($R^2 = H$, $R^3 = Me$), the 5-substituent was retained as a 3-acetyl group in the product.

3. Complexes of Isoxazoles with Metal Ions

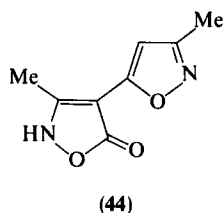
Although isoxazoles are comparatively weak electron donors, complexes with numerous metal ions, notably metal(II) ions, have been described. The ligands include, besides isoxazole and its methyl and phenyl derivatives, aminoisoxazoles and isoxazolones. An account of the analytical and in-

TABLE V
METAL COMPLEXES OF ISOXAZOLES

Ligand	Metal ion ^a	Reference
Isoxazole	Cu, Ag(I), Zn, Cd, Hg, Cr(III), Mn, Fe, Co, Ni, Pd, Pt	129-134
5-Methylisoxazole	Cu, Ag(I), Zn, Co, Ni	135
3,5-Dimethylisoxazole	Cu, Cu(I), Zn, Cd, Hg, Cr, Cr(III), Co, Ni, Pd, Pt	131-133, 136-138
3-Methyl-5-phenylisoxazole	Cu, Cu(I), Zn, Cd, Hg, Cr, Cr(III), Co, Ni, Pd, Pt	133, 138-141
3,5-Diphenylisoxazole	Cu, Zn, Cd, Hg, Cr(III), Co, Ni, Pd, Pt	133, 137, 139, 141, 142
3-Amino-5-methylisoxazole	Cu, Zn, Cd, Hg, Co, Ni, Pd, Pt	143-146
4-Amino-3,5-dimethylisoxazole	Zn, Cd, Hg, Pd, Pt	139, 147
5-Amino-3,4-dimethylisoxazole	Cu, Zn, Cd, Hg, Co, Pd, Pt	144, 145, 148
3-Phenylisoxazol-5(4H)-one	Cu, UO ₂	149
"Dimethyldiisoxazolone" (44) ^b	Cu, Co, UO ₂	150

^a M(II) unless otherwise stated.

^b Structure 44 is



organic chemistry of these complexes is beyond the scope of this review, but they are listed, with references, in Table V.¹²⁹⁻¹⁵⁰

B. REACTIONS OF ISOXAZOLES AND ISOXAZOLIUM SALTS WITH NUCLEOPHILES

1. Reactions of Isoxazoles

Isoxazoles are susceptible to attack by nucleophilic reagents, and the ensuing reactions can take a number of courses, involving initially (a) nucleophilic replacement of a substituent, (b) nucleophilic addition to the ring, and (c) deprotonation. Furthermore, thermal or photochemical ring transformations may precede reaction with a nucleophile (see Section III.C).

Nucleophilic replacement of hydrogen on an isoxazole (cf. the Chichibabin reaction) is unknown, and only a few examples of replacement of substituents such as halogen have been reported.^{1,151} The activated methoxy group in compound **45** is displaced by dimethylamine, and even by phenylmagnesium bromide, in which case the product is **46**.¹⁵²

¹²⁹ W. L. Driessen and P. H. van der Voort, *Inorg. Chim. Acta* **21**, 217 (1977).

¹³⁰ A. Cristini, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **36**, 2473 (1974).

¹³¹ R. Pinna, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **37**, 1681 (1975).

¹³² M. Massacesi, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **38**, 1556 (1976).

¹³³ C. Preti, G. Tosi, M. Massacesi, and G. Ponticelli, *Spectrochim. Acta, Part A* **32**, 1779 (1976).

¹³⁴ J. Kulig and B. Lenarcik, *Pol. J. Chem.* **52**, 477 (1978).

¹³⁵ B. Lenarcik and J. Kulig, *Rocz. Chem.* **51**, 637 (1977).

¹³⁶ G. Devoto, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **37**, 1635 (1975).

¹³⁷ K. J. Oliver, T. N. Waters, D. F. Cook, and C. E. F. Rickard, *Inorg. Chim. Acta* **24**, 85 (1977).

¹³⁸ A. D. Garnovskii, B. G. Gribov, and S. D. Sokolov, *Zh. Obshch. Khim.* **48**, 418 (1978).

¹³⁹ R. Pinna, G. Ponticelli, C. Preti, and G. Tosi, *Transition Met. Chem.* **1**, 173 (1976).

¹⁴⁰ M. Massacesi, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **37**, 1641 (1975).

¹⁴¹ G. Devoto, G. Ponticelli, C. Preti, and G. Tosi, *J. Inorg. Nucl. Chem.* **38**, 1744 (1976).

¹⁴² G. Devoto, M. Massacesi, G. Ponticelli, and C. Preti, *J. Inorg. Nucl. Chem.* **39**, 271 (1977).

¹⁴³ M. Biddau, G. Devoto, M. Massacesi, and G. Ponticelli, *Transition Met. Chem.* **1**, 295 (1976).

¹⁴⁴ M. Biddau, G. Devoto, M. Massacesi, and G. Ponticelli, *Transition Met. Chem.* **1**, 99 (1976).

¹⁴⁵ G. Devoto, M. Massacesi, G. Ponticelli, and R. Ruggeri, *J. Inorg. Nucl. Chem.* **39**, 355 (1977).

¹⁴⁶ G. Devoto, M. Massacesi, R. Pinna, and G. Ponticelli, *Transition Met. Chem.* **2**, 236 (1977).

¹⁴⁷ G. Ponticelli, *J. Inorg. Nucl. Chem.* **39**, 45 (1977).

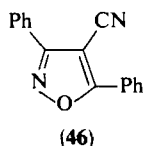
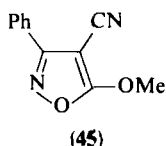
¹⁴⁸ M. Biddau, M. Massacesi, R. Pinna, and G. Ponticelli, *Transition Met. Chem.* **2**, 5 (1977).

¹⁴⁹ N. N. Ghosh, G. N. Mukhopadhyay, and P. C. Chaudhury, *J. Indian Chem. Soc.* **54**, 536 (1977).

¹⁵⁰ N. N. Ghosh and P. C. Chaudhury, *J. Indian Chem. Soc.* **53**, 439 and 779 (1976).

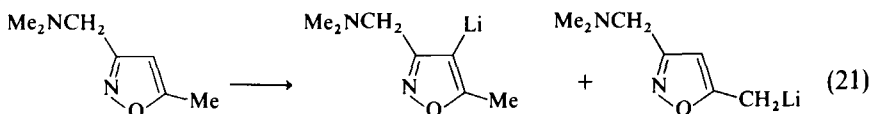
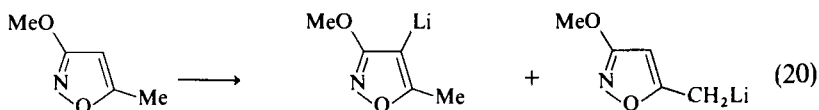
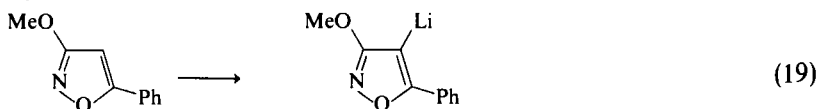
¹⁵¹ G. Adembri and P. Tedeschi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 203 (1965); *Chem. Abstr.* **63**, 13234 (1965).

¹⁵² S. Mangiavacchi and M. Scotton, *Ann. Chim. (Rome)* **63**, 613 (1973).



It is often difficult to identify reactions involving addition to the ring if they are rapidly followed by elimination or ring cleavage. The only examples where the products of simple nucleophilic addition have been isolated involve isoxazolium salts.

Hydrogen atoms at the 3- and 5-positions of isoxazoles are readily removed as protons. Such reactions, with nucleophilic reagents acting as bases, usually result in ring opening. When the 3- and 5-positions are blocked, deprotonation at an unsubstituted 4-position can lead to metallation by, for example, *n*-butyllithium, as in Eqs. (19)–(21).^{153–155}



In the examples of Eqs. (20) and (21), metallation at a 5-methyl group (see Section III,E,2) is in competition with metallation of the ring, despite the presence of 3-substituents favoring the latter.

The reaction of 3-unsubstituted isoxazoles with bases, leading to ring opening, has been known for almost 90 years, and has many applications. The mechanism of the reactions with hydroxide ion has been studied by Italian workers.^{156,157} The reactions showed second-order kinetics (first-order in base and in substrate) and the UV spectra of reaction mixtures showed sharp isosbestic points, indicating the transformation of reactants into products without formation of an intermediate. A primary deuterium isotope effect indicated that fission of the C3—H bond was rate-determining.

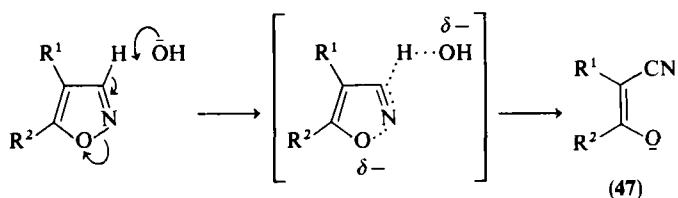
¹⁵³ R. G. Micetich and C. G. Chin, *Can. J. Chem.* **48**, 1371 (1970).

¹⁵⁴ K. Bowden, G. Crank, and W. J. Ross, *J. Chem. Soc. C* p. 172 (1968).

¹⁵⁵ J. Gainer, G. A. Howarth, W. Hoyle, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. I* 994 (1976).

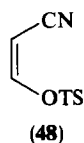
¹⁵⁶ V. Bertini, A. De Munno, and P. Pino, *Gazz. Chim. Ital.* **97**, 173 and 185 (1967).

¹⁵⁷ A. De Munno, V. Bertini, and F. Lucchesini, *J. Chem. Soc., Perkin Trans. 2*, 1121 (1977).

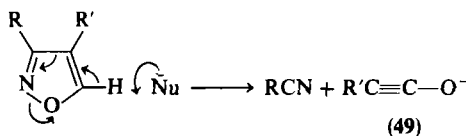


SCHEME 6

Electron-withdrawing substituents accelerated the reaction, but the effect of a 4-aryl group was greater than that of a 5-aryl group. The last observation was consistent with stabilization of a transition state in which negative charge resides on the ring oxygen. The evidence is thus in favor of the E2-type mechanism shown in Scheme 6, rather than an E1cB mechanism in which deprotonation precedes fast ring opening. The primary product of the ring opening is the *cis*-cyanoenolate ion **47**. The fate of this product depends on the substituents and on the conditions. Most of the reported reactions involve protonation, giving the β -ketonitrile (which may or may not be isolable), frequently followed by further reactions of this intermediate *in situ*. Many of these reactions were surveyed by Kochetkov,¹ but an important recent development is the observation that at low temperatures (-40° in the case of isoxazole itself) the *cis* geometry of the enolate is maintained, enabling valuable *cis*-cyanoenol derivatives such as **48** to be prepared in high yield.¹⁵⁸

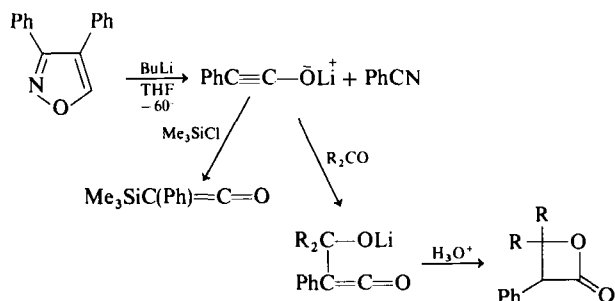


When the 3-position of the isoxazole is blocked, but the 5-position free, ring opening is again either concurrent with deprotonation or takes place under very mild conditions. In these substrates fission of both the N—O bond and the C3—C4 bond occurs, giving a nitrile and an ynone ion (**49**). The latter is usually hydrolyzed on work-up to a carboxylic acid, $R'CH_2CO_2H$,¹ but can be trapped at low temperatures. As exemplified by Scheme 7, such reactions could provide useful syntheses of ketenes and β -lactones.¹⁵⁹



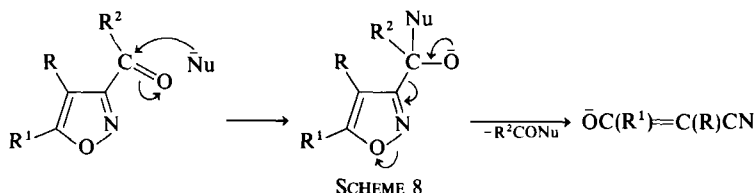
¹⁵⁸ E. J. Hessler, *J. Org. Chem.* **41**, 1828 (1976).

¹⁵⁹ U. Schöllkopf and I. Hoppe, *Angew. Chem., Int. Ed. Engl.* **14**, 765 (1975).



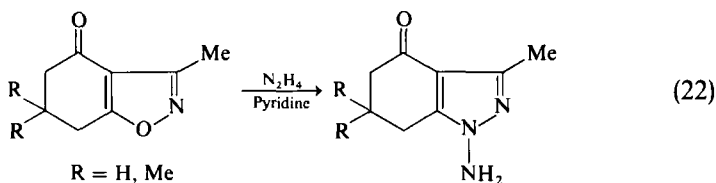
SCHEME 7

3,5-Disubstituted and trisubstituted isoxazoles are in general comparatively resistant to nucleophilic attack, and many of the reported examples involve rearrangement of the isoxazole before reaction with the nucleophile (see Section III,C). However, if electron-withdrawing substituents are present, reaction is facilitated.¹ In compounds with 3-acyl substituents, reaction probably occurs via attack at the carbonyl group (Scheme 8). Such reactions can occur even in the absence of a 5-substituent. In other cases, a mechanism



SCHEME 8

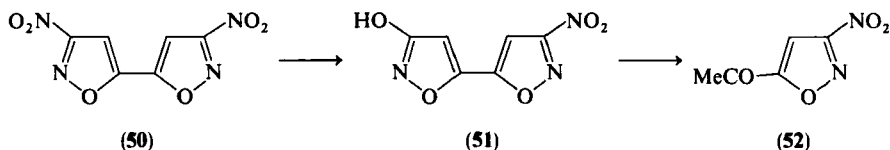
involving nucleophilic addition to the ring seems likely, though evidence so far is lacking. A remarkable example, where attack on the ring is apparently preferred to attack at a carbonyl group, is shown in Eq. (22).¹⁶⁰



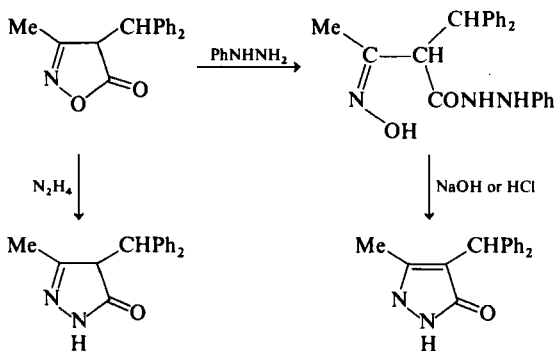
Another interesting example is the alkaline hydrolysis of the bi-isoxazolyl **50**, which proceeds first by nucleophilic displacement of a nitro group giving **51** and then by fission to give 5-acetyl-3-nitroisoxazole (**52**).¹⁶¹ Examples of other reactions of nucleophiles with isoxazol-5(4H)-ones which also lead to

¹⁶⁰ A. A. Akhrem, A. M. Moiseyenko, M. B. Andaburskaya, and A. J. Strakov, *J. Prakt. Chem.* **314**, 31 (1972). However, the at first sight more reasonable hydrazone structure is not ruled out, according to preliminary results from the laboratory of the Editors.

¹⁶¹ E. Duranti, *Studi Urbinate, Fac. Farm.* **45**, 65 (1972); *Chem. Abstr.* **82**, 72851 (1975).



ring opening and sometimes consequent ring transformation are shown in Scheme 9. Others have been briefly reviewed, together with analogous reactions of aminoisoxazoles.¹⁶²⁻¹⁶⁴



SCHEME 9

2. Reactions of Isoxazolium Salts

Isoxazolium salts are even more susceptible than isoxazoles to attack by nucleophiles. It was discovered in the early years of this century that 3-unsubstituted isoxazolium salts were cleaved by a variety of mild reagents, including even carboxylate ions in aqueous solution.^{1,165} However, it was not until much later that the Harvard group were able to elucidate details of the structures of the products and the routes by which they are formed, and to exploit the reactions, notably in peptide synthesis.

The establishment of the main features of the reactions of carboxylate ions with 3-unsubstituted isoxazolium salts is fully described in the classic paper by Woodward and Olofson.¹⁶⁵ A generalized reaction scheme is shown as Scheme 10. Deprotonation at the 3-position is rapidly followed (or more probably accompanied) by ring opening to give the ketoketenimine (54). Ketoketenimines have been detected spectroscopically and are sufficiently stable for isolation in some cases.^{166,167} Reaction of carboxylic acid

¹⁶² T. Nishiwaki, *Synthesis* p. 20 (1975).

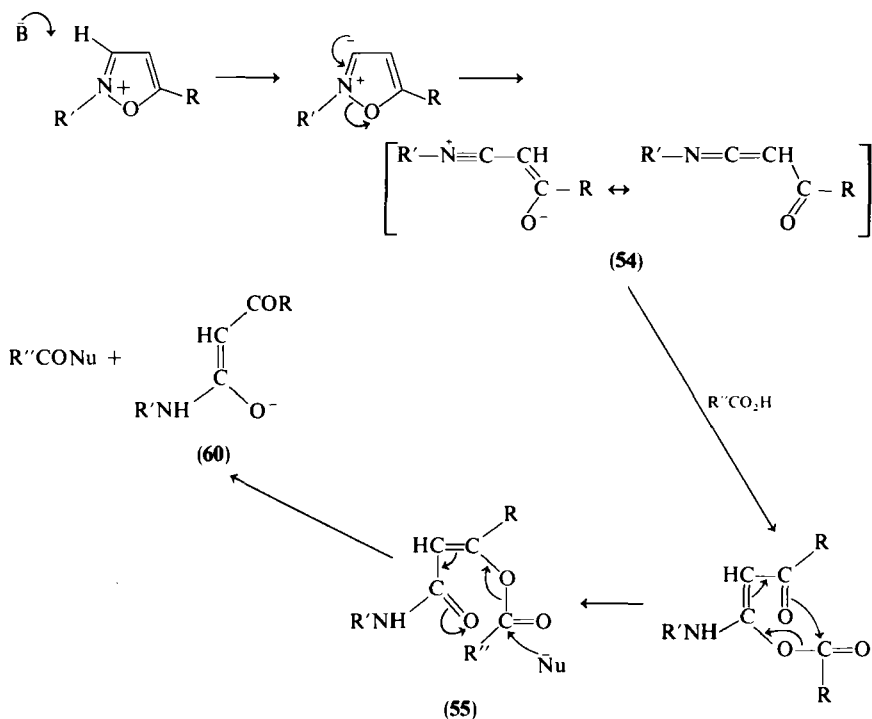
¹⁶³ F. De Sarlo and G. Renzi, *Tetrahedron* **22**, 2995 (1966).

¹⁶⁴ A. Mustafa, W. Asker, A. H. Harhash, and N. A. Kassab, *Tetrahedron* **19**, 1577 (1963).

¹⁶⁵ R. B. Woodward and R. A. Olofson, *Tetrahedron, Suppl.* **7**, 415 (1966).

¹⁶⁶ H. G. Aurich and G. Blinne, *Chem. Ber.* **107**, 13 (1974).

¹⁶⁷ R. B. Woodward and D. J. Woodman, *J. Am. Chem. Soc.* **88**, 3169 (1966).



SCHEME 10

(or carboxylate) with the ketenimine is then followed by transacylation, giving an enol ester (55). The enol ester may then be attacked by a nucleophile as indicated in Scheme 10. If the nucleophile is an amine the final product is an amide; the particular utility of this series of reactions is in peptide synthesis.¹⁶⁸ The preparation of the enol ester and its reaction with a protected amino acid can be carried out in sequence, or the isoxazolium salt may be used as a coupling reagent in a one-pot reaction. References to details of the use of these reactions in the synthesis of peptides may be found in Woodward *et al.*^{168,169}

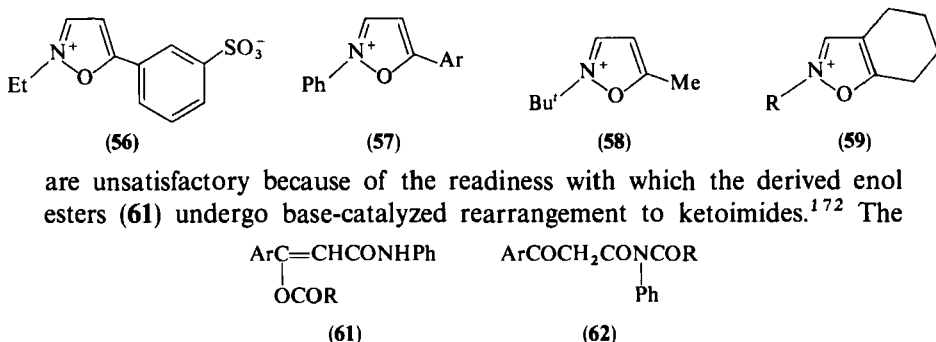
Some examples of the isoxazolium ions which have been tried as peptide coupling reagents are compounds 56–59. The sulfonium inner salt 56 (Woodward's Reagent K) is widely used because the by-product (60) in Scheme 10 is water soluble; it is stated to be superior to diimides as far as racemization is concerned.^{168,170,171} *N*-Arylisoxazolium salts such as 57

¹⁶⁸ R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron, Suppl.* **8**, 321 (1966).

¹⁶⁹ Specialist Periodical Reports, "Aminoacids, Peptides, and Proteins," Vols. 1–8. Chem. Society, London 1968–1976.

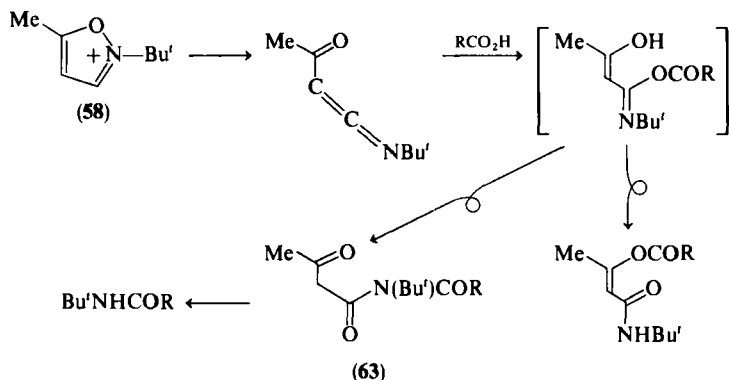
¹⁷⁰ B. Halpern, L. F. Chew, and B. Weinstein, *J. Am. Chem. Soc.* **89**, 5051 (1967).

¹⁷¹ R. A. Olofson and Y. L. Marino, *Tetrahedron* **26**, 1779 (1970).



are unsatisfactory because of the readiness with which the derived enol esters (61) undergo base-catalyzed rearrangement to ketoimides.¹⁷² The

N-*t*-butyl derivatives (e.g., 58) can give satisfactory results but are prone to a number of side reactions, including that just mentioned.¹⁷³⁻¹⁷⁵ Diacylamides (63) may arise as by-products from the ketoketenimine via an iminoanhydride (as shown in Scheme 11) rather than from the enol ester.¹⁷⁶ Tetrahydrobenzisoaxazolium ions (59) and related compounds are promising as far as freedom from rearrangement and lack of promotion of racemization are concerned, but they do not appear to have been evaluated in actual peptide syntheses.¹⁷¹ Although beyond the scope of this review, benzisoxazolium salts have also been applied as reagents for peptide synthesis.^{177,178}



SCHEME 11

¹⁷² R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.* **32**, 388 (1967).

¹⁷³ R. B. Woodward and D. J. Woodman, *J. Org. Chem.* **34**, 2742 (1969).

¹⁷⁴ K. L. Shepard, W. Halczenko, and E. J. Cragoe, *J. Heterocycl. Chem.* **13**, 1219 (1976).

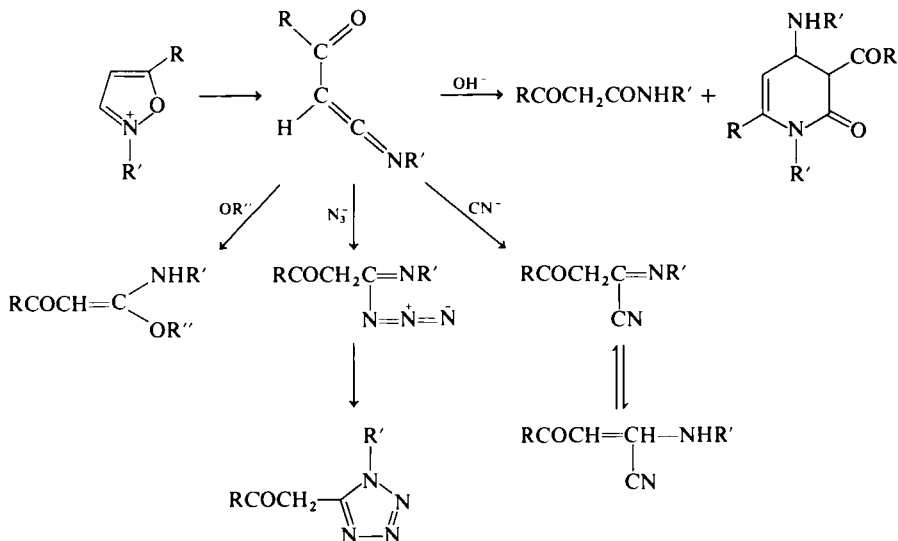
¹⁷⁵ R. B. Woodward and D. J. Woodman, *J. Am. Chem. Soc.* **90**, 1371 (1968).

¹⁷⁶ D. J. Woodman and A. I. Davidson, *J. Org. Chem.* **35**, 83 (1970); **38**, 4288 (1973).

¹⁷⁷ T. R. Govindachari, S. Rajappa, A. S. Akerbar, and S. Iyer, *Indian J. Chem.* **6**, 557 (1968).

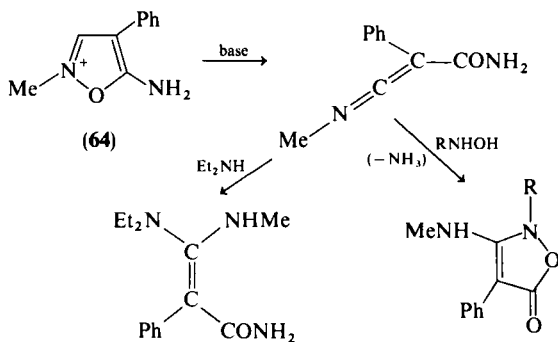
¹⁷⁸ D. S. Kemp, S.-W. Wang, R. C. Mollan, S.-L. Hsia, and P. N. Confalone, *Tetrahedron* **30**, 3766 (1974); D. S. Kemp, S.-W. Wang, J. Rebek, R. C. Mollan, C. Banquer, and S. Subramanyam, *ibid.* p. 3955; D. S. Kemp, S. J. Wrobel, S.-W. Wang, Z. Bernstein, and J. Rebek, *ibid.* p. 3969.

Nucleophiles other than carboxylate ions have been less widely studied in reactions with 3-unsubstituted isoxazolium salts, but they can in general be rationalized in terms of the ketoketenimine intermediate. Examples are shown in Scheme 12. Many of these reactions were recorded in the earlier literature, but the structures of the products were in some cases not established until spectroscopic methods became available.¹⁶⁵ The application of



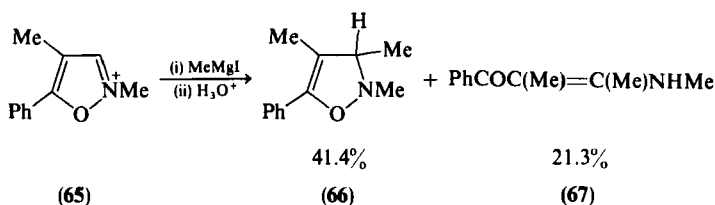
SCHEME 12

such reactions to isoxazoles bearing substituents other than alkyl and aryl groups is little explored, but is exemplified by the reactions of the amino-isoxazolium salt **64** shown in Scheme 13.¹⁶⁶



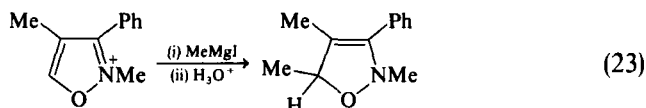
SCHEME 13

With some nucleophiles addition to the ring as well as or instead of ring cleavage has been observed. For example, the reaction of methylmagnesium

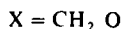
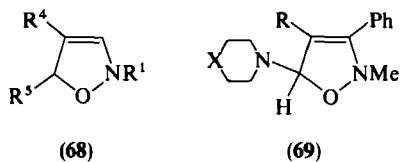


iodide with the isoxazolium ion **65** gave the adduct **66** as well as the ring-cleavage product **67**; with benzyl- and allylmagnesium halides, the adducts were obtained in high yields.¹⁷⁹

When the 3-position was blocked and the 5-position free, nucleophilic attack occurred at the latter, leading to Δ^3 -isoxazolines as exemplified by Eq. (23).¹⁸⁰



3-Unsubstituted isoxazolium salts reacted with borohydride to give isoxazolines (**68**) (and their borane complexes); 3-substituted-5-unsaturated isoxazolium salts gave isoxazolines and, finally, isoxazolidines.¹⁸¹ Most other nucleophiles (e.g., ethoxide, hydroxide, and amines) gave only products of ring cleavage, though in the case of piperidine and morpholine the adducts **69** could be isolated at low temperatures.¹⁸⁰ It is thus possible that in these



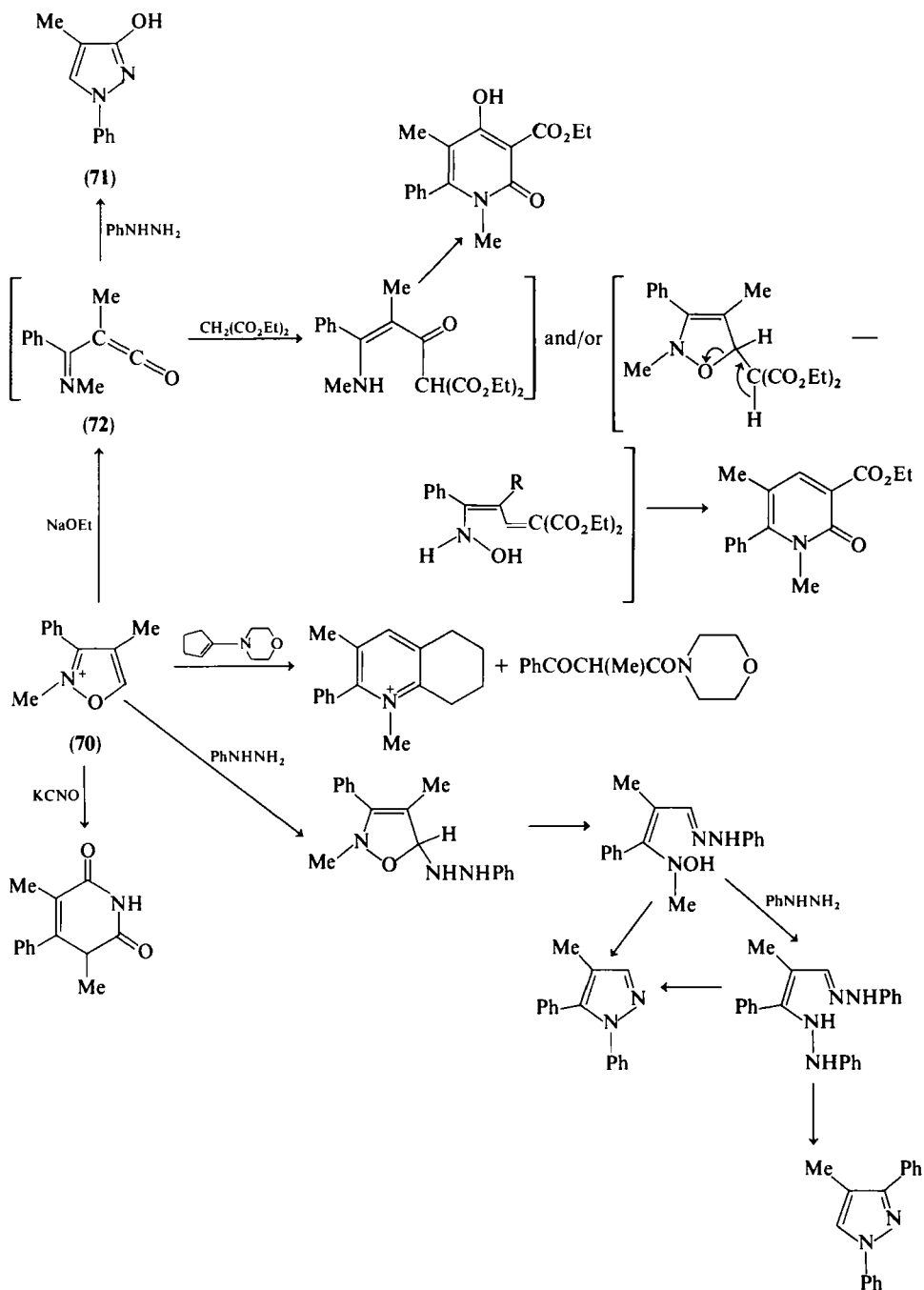
cases ring cleavage occurs via the adducts, although the alternative pathway involving proton abstraction as the initial step cannot be excluded.

Some reactions of 2,3,4-trisubstituted isoxazolium salts (exemplified by **70**) leading to ring transformations, are summarized in Scheme 14.¹⁸⁰ Other "active methylene" compounds such as ethyl acetoacetate and cyanoacetamide give analogous results to those with diethyl malonate; products of base-induced ring opening by ethoxide are also obtained. When the reaction with phenylhydrazine is carried out in the presence of sodium hydroxide in ethanol the product is **71**, presumably formed via the iminoketene **72**.

¹⁷⁹ I. Adachi, K. Harada, and H. Kano, *Tetrahedron Lett.* p. 4875 (1969).

¹⁸⁰ I. Adachi and H. Kano, *Chem. Pharm. Bull.* **17**, 2201 (1969); I. Adachi, K. Harada, R. Miyazuki, and H. Kano, *ibid.* **22**, 61 (1974).

¹⁸¹ I. Adachi, R. Miyazaki, and H. Kano, *Chem. Pharm. Bull.* **22**, 70 (1974).

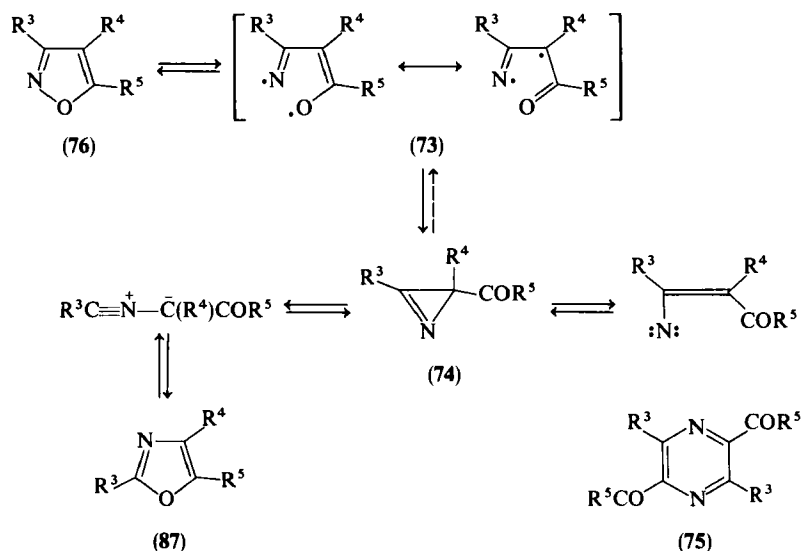


SCHEME 14

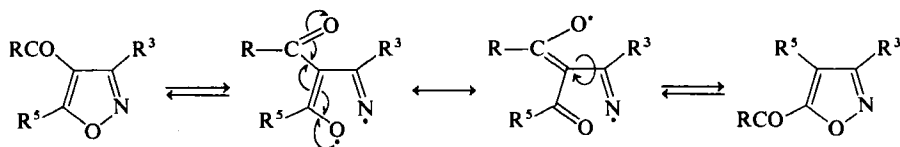
A few examples of nucleophilic substitution of halogen from the 3-position of an isoxazolium salt have been reported.¹⁸²

C. PHOTOLYSIS, THERMOLYSIS, AND ELECTRON-IMPACT INDUCED FRAGMENTATION

Isoxazoles, like other five-membered heterocycles, can undergo a variety of transformations under the influence of light, heat, or electron impact.^{35,36} For isoxazoles, most of the transformations can be rationalized in terms of the pathways shown in Scheme 15. The first step is the fission of the weak N—O bond to give the diradical **73** (or its ionic equivalent). This can then cyclize to give the substituted 2*H*-azirine **74**. Direct evidence for the diradical (**73**) or its equivalent is so far lacking, but some circumstantial evidence is available. The pyrazines (**75**) isolated from some reactions could arise by dimerization of the intermediate.^{183,184} And the ready interchange



SCHEME 15



¹⁸² J. Faust, D. Arndt, and R. Mayer, *Z. Chem.* **8**, 19 (1968).

¹⁸³ T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc. C* p. 1825 (1970).

¹⁸⁴ T. Nishiwaki, T. Saito, S. Onomura, and K. Kondo, *J. Chem. Soc. C* p. 2644 (1971).

of substituents in 4-acylisoxazoles can be explained in terms of the diradical, as shown in Scheme 16.^{185,186}

The formation of the 2*H*-azirine (74) proceeds both photochemically and thermally. In many cases the azirine has been isolated, sometimes in good yield; examples are listed in Table VI.^{183-185,187-196} In other cases it has been intercepted by added reagents, usually nucleophiles. For example, in

TABLE VI
ISOMERIZATION OF ISOXAZOLES (76) TO AZIRINES (74)

R ³	R ⁴	R ⁵	Type of reaction ^a	Yield of azirine (%)	Reference
Me	H	Me	P	14	187
Ph	H	NH ₂	P	42	183
			T	19	
<i>p</i> -ClC ₆ H ₄	H	NH ₂	P	28	188
Ph	H	NHAr	P	53-67	189
			T	ca. 17	
Ar ^b	H	OR'	T ^c	50-72	190
<i>p</i> -MeOC ₆ H ₄	H	Ph	P	35	191
Ph	H	α -C ₁₀ H ₇	P	22	192
Me	H	Ph	P	25	192
Ph	H	Ph	P	25	192
Ph	Ph	NH ₂	P	8	193
			T	73	
Ph	Me	NH ₂	P	18	184
			T	28	
Ph	Me	N(Me)NMe ₂	T	50	194
Ph	Ph	N(Me)NMe ₂	T	71	194
Ph	C(Me)=CHCO ₂ CH ₂ CF ₃	Me	P	15	185
Ph	H	H	P	ca. 10	195

^a P = photochemical, T = thermal.

^b 5-Alkoxyisoxazoles lacking the 3-aryl substituent are much more thermally stable.

^c The reaction is catalyzed by copper(I) stearate.¹⁹⁶

¹⁸⁵ K. Dietliker, P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **59**, 2074 (1976).

¹⁸⁶ A. Padwa, E. Chen, and A. Ku, *J. Am. Chem. Soc.* **97**, 6484 (1975).

¹⁸⁷ T. Sato and K. Saito, *J. Chem. Soc., Chem. Commun.* p. 781 (1974).

¹⁸⁸ T. Nishiwaki and T. Saito, *J. Chem. Soc. C* p. 3021 (1971).

¹⁸⁹ T. Nishiwaki and F. Fujiyama, *J. Chem. Soc., Perkin Trans. 1* p. 1456 (1972).

¹⁹⁰ T. Nishiwaki and T. Saito, *Tetrahedron Lett.* p. 2049 (1969); T. Nishiwaki, T. Kitamura, and A. Nakano, *Tetrahedron* **26**, 453 (1970).

¹⁹¹ B. Singh and E. F. Ullman, *J. Am. Chem. Soc.* **89**, 6911 (1967).

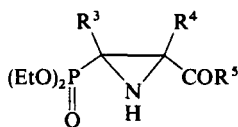
¹⁹² B. Singh, A. Zweig, and J. B. Gallivan, *J. Am. Chem. Soc.* **94**, 1199 (1972).

¹⁹³ T. Nishiwaki and T. Saito, *J. Chem. Soc. C* p. 2648 (1971).

¹⁹⁴ G. Adembri, A. Camparini, F. Ponticelli, and P. Tedeschi, *J. Chem. Soc., Perkin Trans. 1* p. 971 (1977).

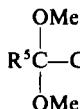
¹⁹⁵ M. Maeda and M. Kojima, *J. Chem. Soc., Perkin Trans. 1* p. 239 (1977).

¹⁹⁶ M. I. Komendatov and R. R. Bekhmukhametov, *Khim. Geterotsikl. Soedin.* p. 1292 (1975).

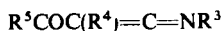


(77)

the presence of arylamines they give *N,N'*-diarylleureas.^{184,197} (The imidazolones previously reported to be formed when 5-aminoisoxazoles were heated alone¹⁹⁸ are almost certainly formed by intermolecular reactions, not via the azirine.^{183,184}) In the presence of triethyl phosphite, aziridinylphosphonates (77) have been obtained.¹⁸⁸ In the presence of alkanols (e.g., methanol) ketals (78) may be obtained, as well as products derived from ketoketenimines (79).¹⁹⁹

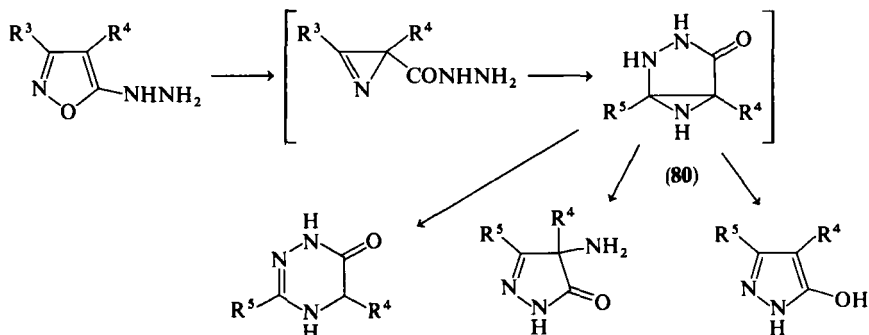


(78)



(79)

In appropriate cases the azirine ring can undergo intramolecular attack by a substituent. Thus, 5-hydrazinoisoxazoles less highly substituted than those included in Table VI give triazinones and pyrazoles implying the intermediate **80** shown in Scheme 17.¹⁹⁴



SCHEME 17

In the absence of traps, the azirines can undergo further transformations that can be rationalized in terms of vinylnitrene or nitrile ylid intermediates.^{185,200-202} Thus, photolysis of 3,4,5-triphenylisoxazole gives some of

¹⁹⁷ T. Nishiwaki, *Chem. Commun.* p. 945 (1970).

¹⁹⁸ H. Kano, *Yakugaku Zasshi* **72**, 150, 1118 (1952).

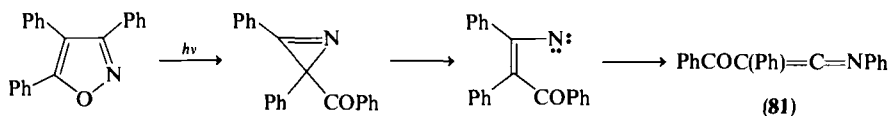
¹⁹⁹ T. Sato, K. Yamamoto, and K. Fukui, *Chem. Lett.* p. 111 (1973).

²⁰⁰ J. P. Ferris and R. W. Trimmer, *J. Org. Chem.* **41**, 13 (1976).

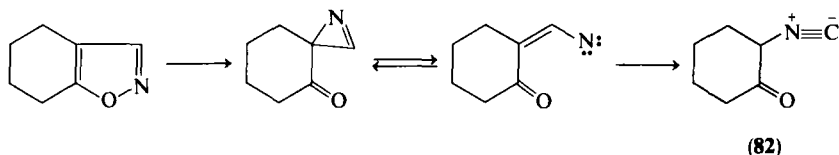
²⁰¹ A. Padwa and P. H. J. Carlsen, *J. Org. Chem.* **41**, 180 (1976).

²⁰² T. Nishiwaki, *J. Chem. Soc., Chem. Commun.* p. 565 (1972).

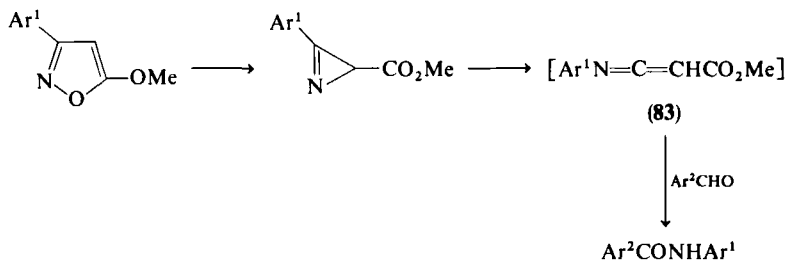
the benzoylketenimine **81** (Scheme 18)²⁰³; hexahydrobenzisoxazole gives the isonitrile **82** (Scheme 19)²⁰⁰; and ketenimines **83** derived from methoxyisoxazoles have been trapped by aromatic aldehydes (Scheme 20).²⁰⁴



SCHEME 18

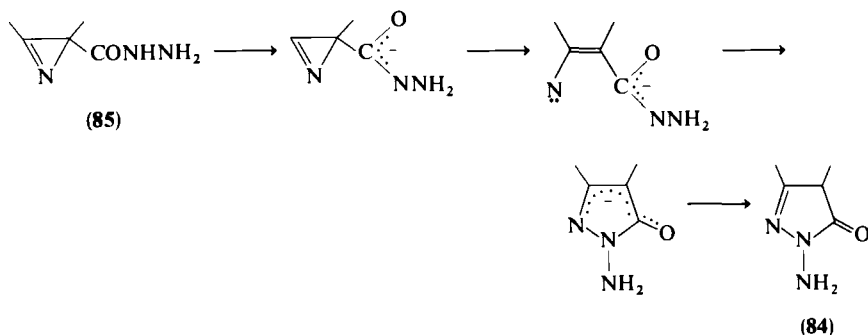


SCHEME 19



SCHEME 20

In the presence of bases 5-hydrazinoisoxazoles give aminopyrazolones (**84**), possibly by deprotonation of the hydrazide **85** followed by cyclization of a nitrene intermediate (Scheme 21).¹⁹⁴

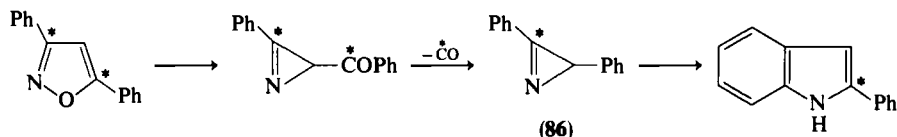


SCHEME 21

²⁰³ M. Kojima and M. Maeda, *Tetrahedron Lett.* p. 2379 (1969).

²⁰⁴ T. Nishiwaki, K. Azechi, and F. Fujiyama, *J. Chem. Soc., Perkin Trans. I* p. 1867 (1974).

On pyrolysis of isoxazoles, decarbonylation has also been observed. Carbon labeling experiments have indicated that the formation of 2,3-diphenyl-2*H*-azirine (**86**) and 2-phenylindole from 3,5-diphenylisoxazole takes place as shown in Scheme 22; thus, 3,5-¹³C-labeled starting material gave 2-[2-¹³C]phenylindole containing 51% of the original ¹³C.²⁰⁵



SCHEME 22

The transformation of the azirine into the oxazole (**87**, Scheme 15) often proceeds at a rate comparable to or faster than its formation from the isoxazole, so that the intermediate can sometimes neither be isolated nor detected. The yields of oxazole are often high, and a variety of functional substituents can be accommodated. Examples are listed in Table VII.^{183,185,186,191,195,200,206-208}

TABLE VII
ISOMERIZATION OF ISOXAZOLES (**76**) INTO OXAZOLES (**87**)

R ³	R ⁴	R ⁵	Conditions ^a	Yield (%)	Reference
Ph	H	H	P	ca. 8	195
Ph	H	Ph	P	79	191
H	—(CH ₂) ₄ —		P	99	200
Ph	COPh	Ph	T	80	186
Ph	C(Me)=CHCO ₂ Me (<i>E</i>)	Me	P	70 (<i>E</i> + <i>Z</i>)	185
OH	H	Ph	P	15	206
OH	H	CHCO ₂ ⁻	P	35 ^b	207
		NH ₃ ⁺			
Ph	H	NH ₂	P	21 ^c	183
Ph	CO ₂ Et	NH ₂	P	20	208

^a P = photochemical, T = thermal.

^b Starting material is ibotenic acid, product is muscazone; see Section V.

^c Product isolated is benzoylaminoacetonitrile.

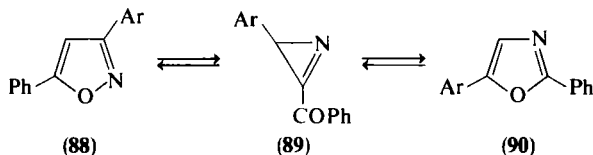
²⁰⁵ G. L. Aldous, J. H. Bowie, and M. J. Thompson, *J. Chem. Soc., Perkin Trans. 1* p. 16 (1976).

²⁰⁶ M. Nakagawa, T. Nakamura, and K. Tomita, *Agric. Biol. Chem.* **38**, 2205 (1974).

²⁰⁷ H. Göth, A. R. Gagneux, C. H. Eugster, and H. Schmid, *Helv. Chim. Acta* **50**, 137 (1967).

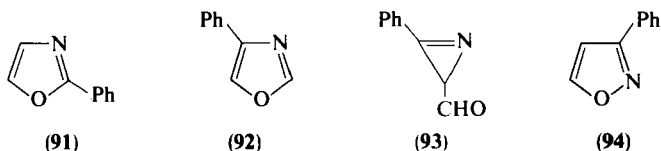
²⁰⁸ H. Wamhoff, *Chem. Ber.* **105**, 748 (1972).

In the discussion above both photochemical and thermal reactions have been referred to. Many of the reactions do proceed under both influences, but there are also many examples where the choice of conditions is important; indeed many of the reactions can be reversed when the conditions are varied. The situation is typified by the system 3,5-diarylloxazole (**88**), azirine (**89**), oxazole (**90**), which has been thoroughly investigated. The

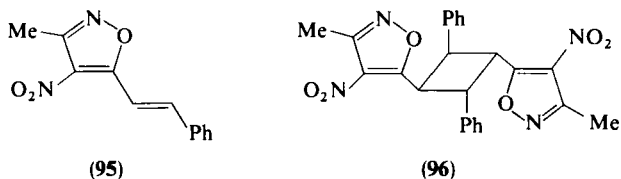


isoxazoles (**88**, Ar = Ph, *p*-MeOC₆H₄) are converted into the corresponding oxazoles (**90**) by light of wavelength ≤ 313 nm, but the reaction is reversed by light ≥ 334 nm.^{191,209} Further studies involving related compounds, emission spectroscopy, sensitization and quenching experiments, and MO calculations, all supported the hypothesis that excitation of the $n \rightarrow \pi^*$ transition of the azirine leads to C—C bond cleavage and subsequent rearrangement to oxazole, while excitation of the lower energy carbonyl $n \rightarrow \pi^*$ transition leads to concerted rearrangement of azirine to isoxazole.¹⁹²

It should be noted that still further complexities may be introduced by the photo and thermal isomerization of the oxazoles.^{35,36} For example, irradiation of 2-phenyloxazole (**91**) gives 4-phenyloxazole (**92**) and 3-phenyl-2*H*-azirine-2-carbaldehyde (**93**); the latter product is transformed thermally, but not photochemically, into 3-phenylisoxazole (**94**).¹⁹⁵



Despite the photolability of isoxazoles, a few photoreactions of functional groups, not involving the disruption of the ring, have been described. For example, irradiation of compound (**95**) in the solid state gives the dimer (**96**).²¹⁰



²⁰⁹ E. F. Ullman and B. Singh, *J. Am. Chem. Soc.* **88**, 1844 (1966).

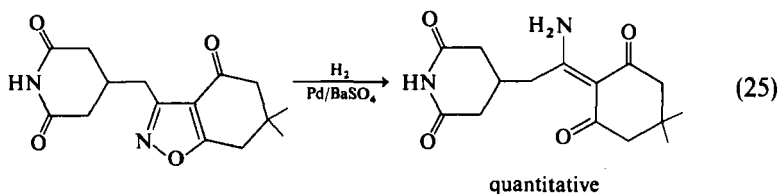
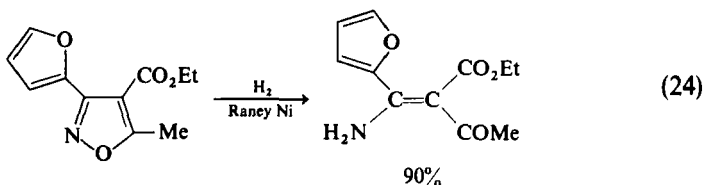
²¹⁰ D. Donati, M. Fiorenza, E. Moschi, and P. Sarti-Fantoni, *J. Heterocycl. Chem.* **14**, 951 (1977).

The previous discussion has referred to photolysis and thermolysis only. Many of the transformations described have also been observed on mass spectrometry of isoxazoles, although it is not always clear whether they occur as a result of electron impact or by prior thermal reaction.^{211-212a} It should be noted that such reactions can create problems in the use of mass spectrometry for elucidating the structures of isoxazoles.

D. REDUCTIVE CLEAVAGE

Early work on isoxazoles revealed that they were readily cleaved under reducing conditions; by the time of the earlier review many examples were known, but the potential of these reactions in synthesis was only beginning to be realized.¹ Since then the isoxazole ring has become a major tool as a masked 1,3-dicarbonyl compound or enaminoketone, particularly for the synthesis of homo- and heterocycles.²¹³

In the earlier work various reducing agents were used.¹ Catalytic hydrogenolysis is now almost always employed; some examples illustrating the high yields attainable and the compatibility with other functional groups are shown in Eqs. (24)–(26).²¹⁴⁻²¹⁶



²¹¹ T. Nishiwaki, *Tetrahedron* **25**, 747 (1969); *Org. Mass Spectrom.* **5**, 123 (1971).

²¹² J. H. Bowie, R. K. M. R. Kallury, and R. G. Cooks, *Aust. J. Chem.* **22**, 563 (1969); R. A. Khmel'nitskii, K. K. Zhigulev, and S. D. Sokolov, *Izv. Timiryazevsk. Skh. Akad.* No. 1, p. 197 (1971); *Chem. Abstr.* **74**, 140381 (1971).

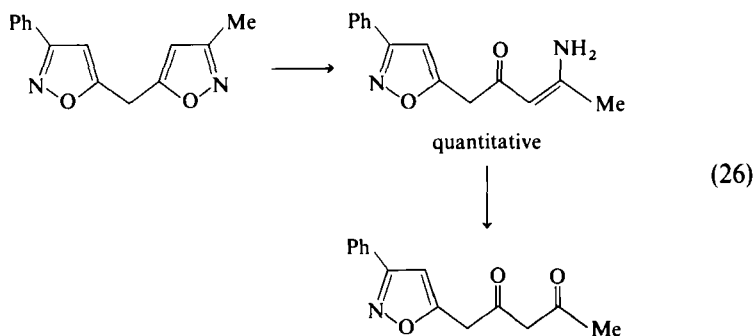
^{212a} J.-L. Aubagnac and D. Bourgeon, *Org. Mass Spectrom.* **12**, 65 (1977).

²¹³ A. I. Meyers, "Heterocycles in Organic Synthesis," Wiley (Interscience), New York, 1974.

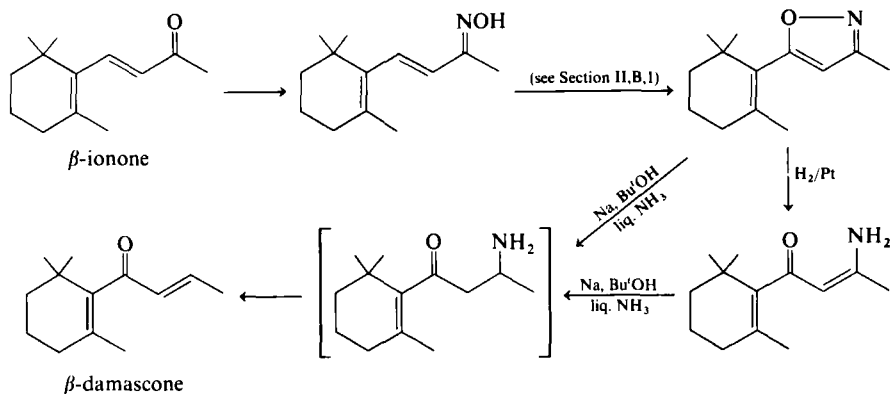
²¹⁴ D. N. McGregor, U. Corbin, J. E. Swigor, and L. C. Cheney, *Tetrahedron* **25**, 389 (1969).

²¹⁵ A. A. Akhrem, F. A. Lakhvich, V. A. Khrpach, and I. B. Klebanovich, *Tetrahedron Lett.* p. 3983 (1976).

²¹⁶ S. Auricchio, S. Morrocchi, and A. Ricca, *Tetrahedron Lett.* p. 2793 (1974).



The enaminoketones thus obtained may then be transformed, sometimes *in situ*, in a number of useful ways. For example, reaction with phosphorus pentasulfide gives isothiazoles, thus providing a method for converting isoxazoles into the corresponding isothiazoles.²¹⁴ Under mild conditions hydrolysis of the enaminoketones can give the corresponding 1,3-diketones [see for example Eqs. (25), (26)]. They may also be reduced to aminoketones, which under the conditions used (sodium and *t*-butanol in liquid ammonia) lose ammonia to give the enone; the same reducing system can in fact be used to convert an isoxazole into an enone in one step. The sequence is exemplified in Scheme 23, which illustrates an elegant method for transposing the substituents of a conjugated enone.²¹⁷ If, alternatively, it is

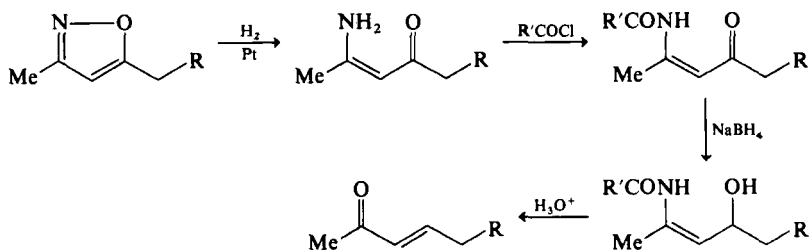


SCHEME 23

desired to protect and then regenerate a conjugated enone (or to convert a 1,3-diketone into an enone), the enaminoketone can first be benzoylated or acylated and then reduced with borohydride and hydrolyzed, as illustrated in Scheme 24.²¹⁸

²¹⁷ G. Büchi and J. C. Vederas, *J. Am. Chem. Soc.* **94**, 9128 (1972).

²¹⁸ C. Kashima, Y. Yamamoto, and Y. Tsuda, *J. Org. Chem.* **40**, 526 (1975).



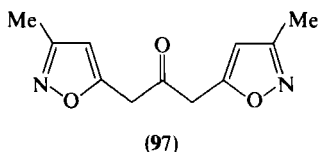
SCHEME 24

Reductive cleavage and hydrolysis of appropriate diisoxazolymethanes leads to 1,3,5,7-tetraketones, which can be used in the biomimetic synthesis of benzenoid compounds, which are formed in nature by the polyketide pathway. Some of these results are summarized in Table VIII. The synthesis of compounds such as (97) has provided a synthetic equivalent of a 1,3,5,7,9-

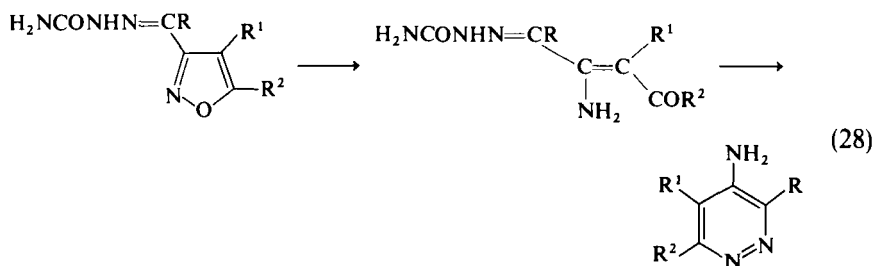
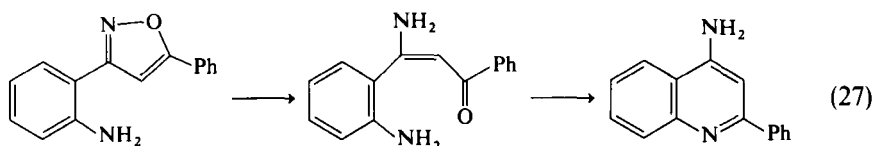
TABLE VIII
SYNTHESIS OF BENZENE DERIVATIVES FROM DIISOXAZOLYMETHANES

Diisoxazolymethane	Product of reductive cleavage	Product of acid cyclization	Reference
			216
			216
			221

pentaketone, and there seems every likelihood that the series could be extended still further.^{219,220}



The most spectacular applications of reductive cleavage of isoxazoles are in the construction of new rings by the intramolecular reaction of the enaminketone produced with suitably placed functional groups. The cyclizations listed in Table VIII^{216,221} may be regarded as examples of this process, and illustrate the fact that amino and carbonyl groups are the functions usually employed. Some examples, illustrating the range of ring systems that may be produced utilizing an amino group, are shown in Eqs. (27)–(31).^{222–228}



²¹⁹ T. Tanaka, M. Mikazaki, and I. Iijima, *J. Chem. Soc., Chem. Commun.* p. 233 (1973).

²²⁰ S. Auricchio, R. Colle, S. Morrocchi, and A. Ricca, *Gazz. Chim. Ital.* **106**, 823 (1976).

²²¹ S. Auricchio, A. Ricca, and O. V. De Pava, *Chim. Ind. (Milan)* **58**, 699 (1976).

²²² G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Gazz. Chim. Ital.* **96**, 1073 (1966).

²²³ V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **57**, 846 (1967); V. Sprio, S. Plescia, and O. Migliari, *ibid.* **61**, 271 (1971).

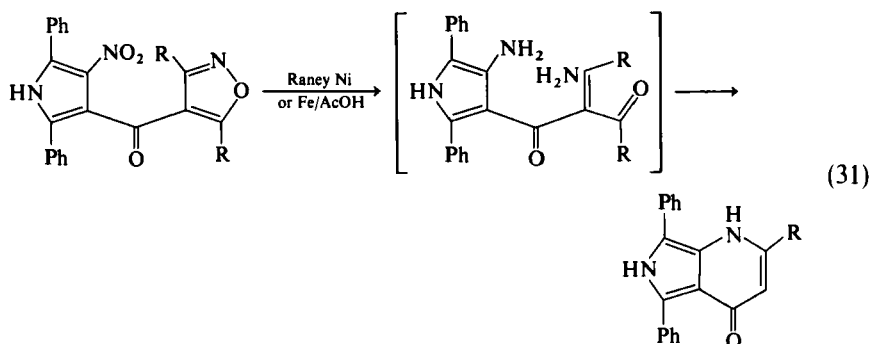
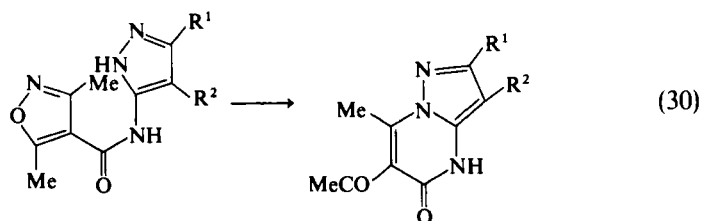
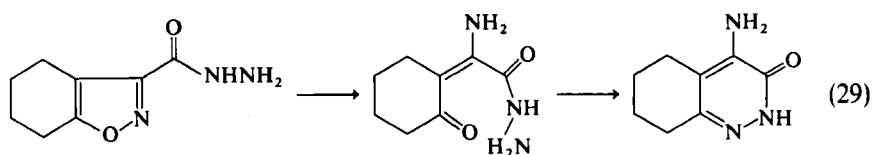
²²⁴ M. Ruccia, N. Vivona, S. Plescia, and V. Sprio, *J. Heterocycl. Chem.* **8**, 289 (1971).

²²⁵ V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **56**, 1103 (1966).

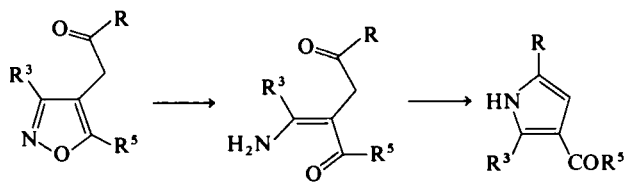
²²⁶ S. Plescia, S. Petruso, and V. Sprio, *J. Heterocycl. Chem.* **11**, 623 (1974).

²²⁷ V. Sprio and S. Plescia, *J. Heterocycl. Chem.* **9**, 951 (1972); E. Ajello, O. Migliari, and V. Sprio, *ibid.* p. 1169.

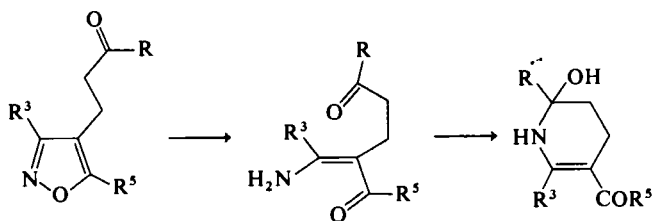
²²⁸ G. Dattolo, E. Aiello, S. Plescia, G. Cirrincione, and G. Daidone, *J. Heterocycl. Chem.* **14**, 1021 (1977).



The most useful cyclizations via intramolecular reaction with a carbonyl group involve 4-(2-oxoalkyl)isoxazoles, leading to pyrroles (Scheme 25) and 4-(3-oxoalkyl)isoxazoles, leading to pyridine derivatives (Scheme 26).

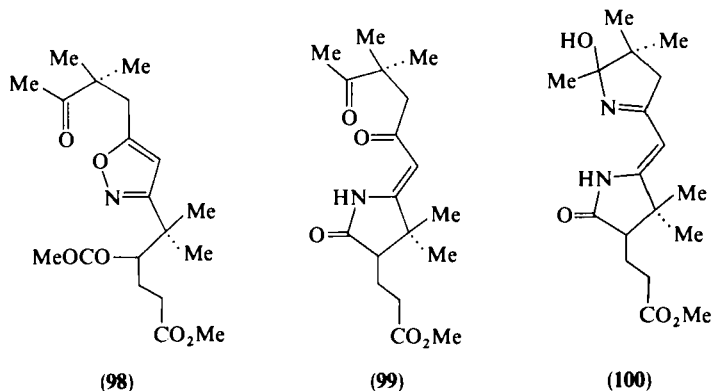


SCHEME 25

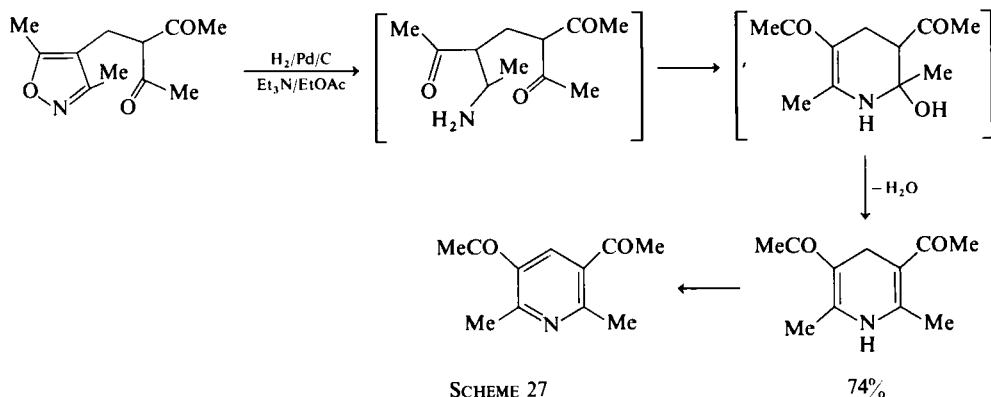


SCHEME 26

A beautiful application of Scheme 25 originated by Cornforth²²⁹ and developed by Stevens^{230,231} is the strategy for synthesizing corrins. The relevant part of the approach used is illustrated by the reduction of the isoxazole (98), prepared from the appropriate nitrile oxide and alkyne (see Section II,C,2), leading, via intramolecular attack on an ester carbonyl, to the intermediate (99), which on treatment with ammonia gave the "semi-corrin" (100).²³¹



In Scheme 26 the product is shown as a cyclic carbinolamine. This can undergo various transformations. Under conditions favoring dehydration, dihydropyridines (which are readily oxidized to pyridines) are obtained, as shown in Scheme 27 and Eq. (32).²³²

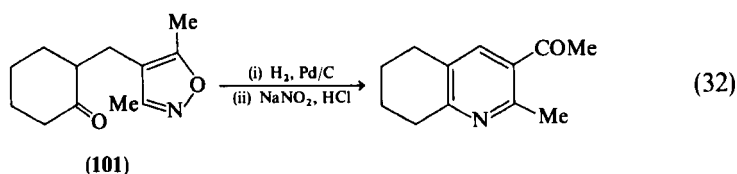


²²⁹ A. H. Jackson and K. H. Smith, in "The Total Synthesis of Natural Products" (J. ApSimon, ed.), Vol. 1, p. 261. Wiley (Interscience), New York, 1973.

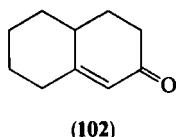
²³⁰ R. V. Stevens, *Tetrahedron* **32**, 1599 (1976).

²³¹ R. V. Stevens, J. M. Fitzpatrick, P. B. Germeraad, B. L. Harrison, and R. Lapalme, *J. Am. Chem. Soc.* **98**, 6313 (1976); R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, *ibid.* p. 6317.

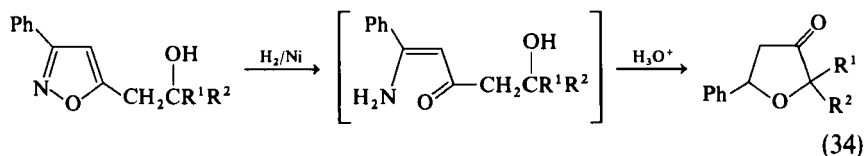
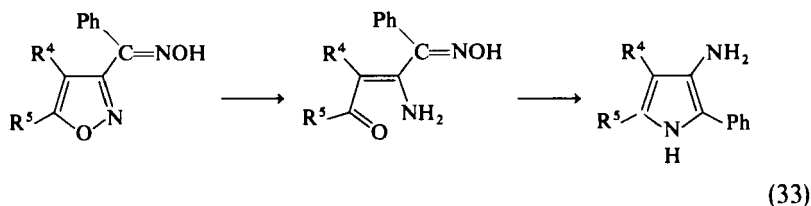
²³² G. Stork, M. Ohashi, H. Kamachi, and H. Kakisawa, *J. Org. Chem.* **36**, 2784 (1971).



Under conditions not favoring dehydration alternative hydrolytic pathways predominate.²³³ Thus, if the carbinolamine derived from compound (101) is treated with aqueous base, the main product is the octalone (102).²³⁴ This annelation clearly has great potential in synthesis, and it has already been exploited in, for example, the construction of the AB ring system of steroids (Stork and McMurry²³⁵; see also Ohashi²³⁶).



A few examples of reductive cleavage followed by cyclization involving groups other than carbonyl or amino have been reported. They include oximes, Eq. (33),²³⁷ alcohols, Eq. (34),²²² and enamines, Eq. (35).²³⁸



²³³ G. Stork and J. E. McMurry, *J. Am. Chem. Soc.* **89**, 5463 (1967).

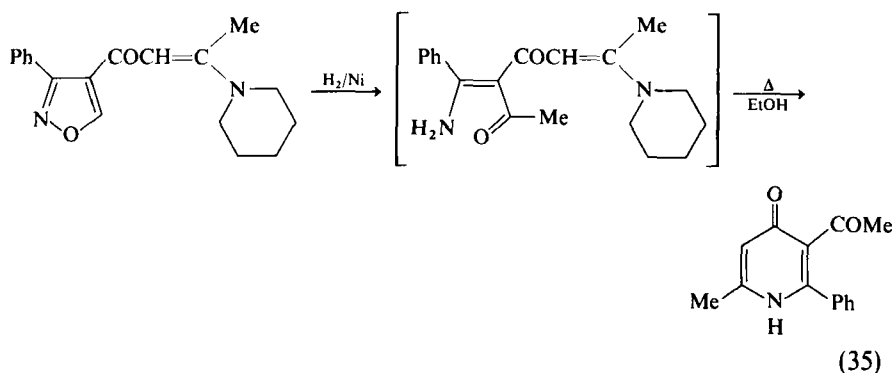
²³⁴ G. Stork, S. Danishefsky, and M. Ohashi, *J. Am. Chem. Soc.* **89**, 5459 (1967).

²³⁵ G. Stork and J. E. McMurry, *J. Am. Chem. Soc.* **89**, 5464 (1967).

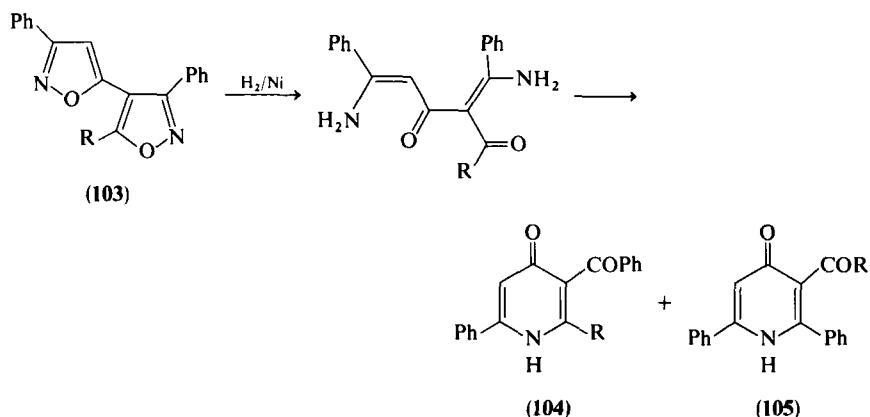
²³⁶ M. Ohashi, *Nippon Kagaku Zasshi* **91**, 12 (1970).

²³⁷ V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **56**, 858 (1966).

²³⁸ P. Caramella and A. Querci, *Synthesis* p. 46 (1972).



An interesting example of a system where both amino-carbonyl and amino-imine cyclizations occur involves the biisoxazolyl (**103**), which on catalytic hydrogenation followed by cyclization gives the pyridones (**104**) and (**105**).²³⁸



E. SPECIAL REACTIONS OF SIDE CHAINS ON ISOXAZOLES

Many of the reactions of functional groups attached to an isoxazole ring are unexceptional. This section is therefore confined to an account of two topics: the first, rearrangements involving three-atom side chains, is of intrinsic interest, and the second, reactions proceeding via deprotonation at an α -carbon atom, is very useful in synthesis.

1. Rearrangements Involving Three-Atom Side Chains

Many rearrangements of derivatives of five-membered heterocycles of the general type (**106**) (or equivalent uncharged molecules), represented by

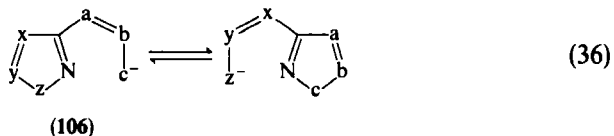
TABLE IX
REARRANGEMENTS INVOLVING THREE-ATOM SIDE CHAINS OF ISOXAZOLES

Starting material	Product	Reference
		240, 241 ^a
		242 ^b ; see, also 241, 243
		244
		245
		246

^a A formally similar rearrangement of isoxazol-5-ones probably proceeds by hydrolysis of the lactone linkage followed by recyclization.²⁴⁷

^b Reaction carried out in presence of hydroxylamine, so product isolated as oxime.

Eq. (36), are known. Some examples involving isoxazole derivatives (106; $x = y = \text{CH}$, $z = \text{O}$) are shown in Table IX. It is noteworthy that many of these examples were known at the time of the earlier review,¹ but their importance was not then apparent. It seems likely that many of these



rearrangements are concerted, though the evidence is far from conclusive.²³⁹ Their scope is not fully explored, but the examples given in Table IX²⁴⁰⁻²⁴⁷ are consistent with the generalization that they require at least one N—O bond in the ring of the starting material and the formation of a C—N, N—N or C—S bond in the product heterocycle.^{239,246} For a given side chain the rate of rearrangement for three systems was 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole.^{246,248} The cyclization of a 3-azidoisoxazole to an isoxazolotetrazole has so far been observed only in the benzo-fused series.²⁴⁹

2. Reactions Proceeding via α -Deprotonation

The acidity of α -hydrogens of 3- and, especially, 5-alkyl side chains on isoxazole rings is enhanced by the ring nitrogen. Aldol-type condensations and related reactions of such groups have been known for many years, but additional activation by electron-withdrawing substituents was regarded as necessary.^{1,250} Later work has shown that by the use of strong bases such as sodamide, alkyl-lithium compounds, and lithium dialkylamides, carbanionic intermediates may be generated from alkylisoxazoles without supplementary activation and caused to react with a variety of electrophilic reagents.^{155,250,251} The reactivity and reactions of 3,5-dimethylisoxazoles have been reviewed.²⁵² Electron-withdrawing 4-substituents, as expected, accelerate deprotonation, while electron-donating 4-substituents retard it.^{252,253} Where both 3- and 5-alkyl groups are present, that in the 5-position is more reactive. Table X lists examples of syntheses involving

²³⁹ A. J. Boulton, *Lect. Heterocycl. Chem.* **2**, 545 (1974).

²⁴⁰ T. Ajello and S. Cusmano, *Gazz. Chim. Ital.* **70**, 770 (1940); T. Ajello and B. Tornetta, *ibid.* **77**, 332 (1947).

²⁴¹ A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C* p. 2005 (1967).

²⁴² T. Ajello, *Gazz. Chim. Ital.* **67**, 779 (1937); T. Ajello and S. Cusmano, *ibid.* **68**, 792 (1938); **69**, 391 (1939); A. Quilico and M. Freri, *ibid.* **76**, 1 (1946).

²⁴³ T. Ajello, V. Sprio, and J. Fabra, *Ric. Sci. Parte 2, Sez. B* **4**, 575 (1964).

²⁴⁴ H. Kano and E. Yamazaki, *Tetrahedron* **20**, 159 (1964).

²⁴⁵ H. Kano and E. Yamazaki, *Tetrahedron* **20**, 461 (1964).

²⁴⁶ N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans. I* p. 1616 (1977).

²⁴⁷ V. M. Belikov, T. F. Savel'eva, and E. N. Safonova, *Izv. Akad. Nauk SSSR, Ser. Khim.* p. 2060 (1973).

²⁴⁸ M. Ruccia, N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans. I* 589 (1977).

²⁴⁹ R. Faure, J.-P. Galy, E.-J. Vincent, and J. Elguero, *J. Heterocycl. Chem.* **14**, 1299 (1977).

²⁵⁰ G. Renzi, V. Dal Piaz, and S. Pinzauti, *Gazz. Chim. Ital.* **99**, 753 (1969).

²⁵¹ R. G. Micetich, *Can. J. Chem.* **48**, 2006 (1970).

²⁵² C. Kashima, Y. Yamamoto, and Y. Tsuda, *Heterocycles* **6**, 805 (1977).

²⁵³ S. D. Sokolov and V. N. Setkina, *Khim. Geterotsikl. Soedin.* p. 786 (1969); p. 377 (1968).

TABLE X
BASE-INDUCED REACTIONS OF 3,5-DIMETHYLISOXAZOLE
WITH ELECTROPHILIC REAGENTS

Base	Electrophilic reagent	5-Substituent in product ^a	Reference
Bu ⁿ Li	D ₂ O	CH ₂ D	252
NaNH ₂ , Bu ⁿ Li	Mel ^b	CH ₂ CH ₃ ^c	251, 252
Bu ⁿ Li	CO ₂	CH ₂ CO ₂ H	251
NaNH ₂ , LiNH ₂	R ¹ R ² CO	CH ₂ CR ¹ (R ²)OH	252, 254
Bu ⁿ Li	RCOCl ^d	CH ₂ COR	220
NaNH ₂	PhCH=NPh	CH ₂ CH(Ph)NHPh ^e	252, 255
NaNH ₂	PhCN	CH=C(NH ₂)Ph ^f	252, 255
Bu ⁿ Li	MeSCl	CH ₂ SMe	256

^a After hydrolysis, where appropriate.

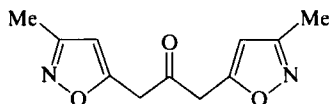
^b Similarly with other alkyl halides.

^c With an excess of sodamide and iodomethane 3-methyl-5-*t*-butylisoxazole can be obtained.

^d With phosgene, the ketone (110) is obtained.

^e Some disubstitution observed.

^f Readily hydrolyzed to CH₂COPh.



(110)

the reaction of the carbanion derived from 3,5-dimethylisoxazole with electrophiles.^{220,251,252,254-256}

5-Alkylisoxazolium salts are deprotonated even more readily than the corresponding isoxazoles and can undergo condensation reactions under the influence of comparatively weak bases. In these compounds, however, deprotonation of 3-alkyl groups may compete; the ratio of deprotonation in the 3- and 5-substituents is markedly influenced by the nature of the base (see Scheme 28).²³⁶

The *N*-alkyl groups of *N*-alkylisoxazolium salts are also susceptible to α -deprotonation, which may compete with deprotonation of 3-alkyl groups or with nucleophilic addition.^{180,257} The product of deprotonation of the

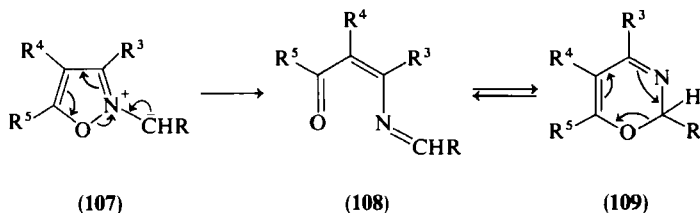
²⁵⁴ C. Kashima, M. Uemori, Y. Tsuda, and Y. Omote, *Bull. Chem. Soc. Jpn.* **49**, 2254 (1976).

²⁵⁵ C. Kashima and Y. Tsuda, *Bull. Chem. Soc. Jpn.* **46**, 3533 (1973).

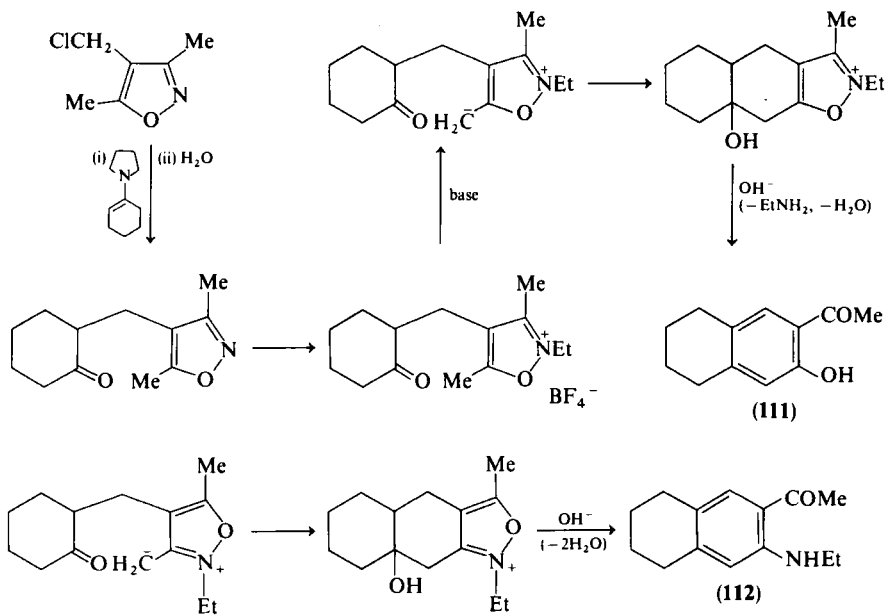
²⁵⁶ P. Bravo and G. Gaviraghi, *J. Heterocycl. Chem.* **14**, 37 (1977).

²⁵⁷ C. Kashima, N. Mukai, Y. Yamamoto, Y. Tsuda, and Y. Omote, *Heterocycles* **7**, 241 (1977).

N-alkyl group is an ylid (107), which can react to give the ring-opened intermediate (108) or 2*H*-1,3-oxazine (109).²⁵⁸



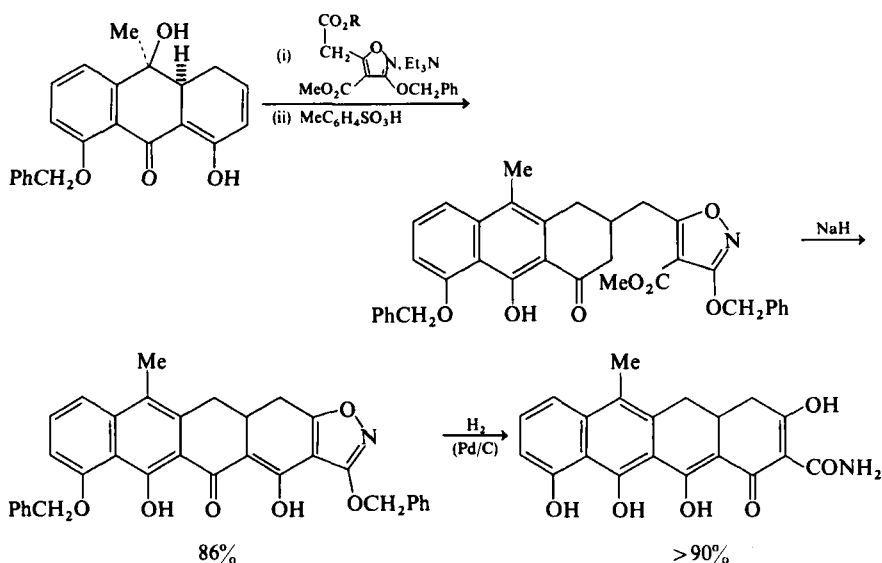
A particularly useful application of the types of reaction described above is the formation of a ring by intramolecular base-induced condensation of a methylisoxazole (or isoxazolium salt) with a conveniently placed carbonyl function. The required starting materials are often conveniently prepared from the 4-chloromethyl derivatives.²³⁶ The initial products can undergo various transformations via cleavage of the isoxazole ring. One of the earliest examples, which illustrates the principles well, is shown in Scheme 28.



SCHEME 28

²⁵⁸ J. F. King and T. Durst, *Can. J. Chem.* **40**, 882 (1962).

When the base used was sodium hydroxide the main product was the phenol (111), formed via deprotonation of the 5-methyl group, whereas with pyrrolidine the product was the amine (112), formed via deprotonation of the 3-methyl group.²⁵⁹ Other similar syntheses have been reviewed.²³⁶ A recent example has shown how a 3-benzyloxyisoxazole derivative could be utilised to "store" the β -ketoamide system of ring A of tetracyclines (Stork and Hagedorn²⁶⁰; see also Boulton *et al.*²⁶¹). One of the model syntheses successfully accomplished is shown in Scheme 29.



SCHEME 29

IV. Physicochemical Studies on Isoxazoles

A. THEORETICAL AND STRUCTURAL STUDIES

Compared with other potentially aromatic five-membered heterocycles, few theoretical studies on isoxazoles have been reported.²⁶² Del Re, using

²⁵⁹ M. Ohashi, T. Maruishi, and H. Kakisawa, *Tetrahedron Lett.* p. 719 (1968).

²⁶⁰ G. Stork and A. A. Hagedorn, *J. Am. Chem. Soc.* **100**, 360 (1978).

²⁶¹ A. J. Boulton, A. R. Katritzky, A. M. Hamid, and S. Oksne, *Tetrahedron* **20**, 2835 (1964).

²⁶² M. J. Cook, A. R. Katritzky and P. Linda, *Adv. Heterocycl. Chem.* **17**, 255 (1974).

a Hückel model and calculating "aromaticity" in terms of delocalization energies or charge transfer, concludes that isoxazole is less aromatic than oxazole, furan, and pyrrole (Del Re²⁶³; see also Del Re *et al.*²⁶⁴). Kamiya concludes from Pariser–Parr–Pople SCF calculations that the total π -energy for isoxazole is similar to that for oxazole, despite the very low π -bond order in isoxazole.²⁶⁵ *Ab initio* all-electron calculations have given some correlation with experimental data (Berthier *et al.*²⁶⁶; see also Mackrodt *et al.*²⁶⁷). The photoelectron spectra of isoxazole and other five-membered heterocycles have been recorded and the molecular core binding energies interpreted in terms of MO calculations.²⁶⁸ An assessment of the empirical resonance energy of isoxazole, derived from the heat of dehydration of 4,5-dihydro-5-hydroxy-3-phenyl-isoxazole indicates that the resonance stabilization is low.²⁶⁹

Surprisingly, the enthalpy of combustion of isoxazole was determined only very recently.²⁷⁰ For isoxazole, ΔH_c° (298.15 K) = $-(394.70 \pm 0.12)$ kcal_{th} mol⁻¹, from which the enthalpy of formation in the gas phase was derived as ΔH_f° (g) = 18.78 ± 0.13 kcal_{th} mol⁻¹. The enthalpies of combustion of 3-amino-5-methylisoxazole and 5-amino-3,4-dimethylisoxazole have also been determined.²⁷¹ Thermodynamic parameters for isoxazole have been derived from vibrational spectra using the harmonic oscillator–rigid rotor approximation.^{272,273} Analysis of the rotational spectra of isotopic forms of isoxazole, studied by double resonance modulated microwave spectroscopy, has given the molecular dimensions shown in Fig. 1.^{274,275}

²⁶³ G. Del Re, "The Jerusalem Symposia on Quantum Chemistry and Biochemistry," Vol. II, p. 74. Isr. Acad. Sci. Humanities, Jerusalem, 1971.

²⁶⁴ G. Del Re, *J. Chem. Soc.* p. 3324 (1962); G. Berthier and G. Del Re, *ibid.* p. 3109 (1965); B. Zurawski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **14**, 481 (1966); *Chem. Abstr.* **66**, 14842 (1967); D. A. Bochvar, A. A. Bagatur'yants, and A. V. Tutkevich, *Izv. Akad. Nauk SSSR, Ser. Khim.* p. 353 (1966).

²⁶⁵ M. Kamiya, *Bull. Chem. Soc. Jpn.* **43**, 3344 (1970).

²⁶⁶ G. Berthier, L. Praud and J. Serre, "The Jerusalem Symposia on Quantum Chemistry and Biochemistry," Vol. I, p. 40. Isr. Acad. Sci. Humanities, Jerusalem, 1970.

²⁶⁷ W. C. Mackrodt, A. Wardley, P. A. Curnuck, N. L. Owen, and J. Sheridan, *Chem. Commun.* p. 692 (1966); D. W. Davies and W. C. Mackrodt, *ibid.* pp. 345 and 1226 (1967).

²⁶⁸ A. D. Baker, D. Betteridge, N.-R. Kemp, and R. E. Kirby, *Anal. Chem.* **42**, 1064 (1970).

²⁶⁹ D. T. Clark and D. M. J. Lilley, *Chem. Phys. Lett.* **9**, 234 (1975).

²⁷⁰ D. G. McCormick and W. S. Hamilton, *J. Chem. Thermodyn.* **10**, 275 (1978).

²⁷¹ W. S. Hamilton and D. A. Ayers, *J. Chem. Eng. Data* **18**, 366 (1973); W. S. Hamilton and G. M. Mitchell, *ibid.* p. 36.

²⁷² T. R. Manley and D. A. Williams, *Spectrochim. Acta, Part A* **24**, 361 (1968).

²⁷³ B. Soptrajanov, *Croat. Chim. Acta* **40**, 79 (1968).

²⁷⁴ O. L. Stiefvater, *J. Chem. Phys.* **63**, 2560 (1975).

²⁷⁵ O. L. Stiefvater, P. Woesberger, and J. Sheridan, *Chem. Phys.* **9**, 435 (1975).

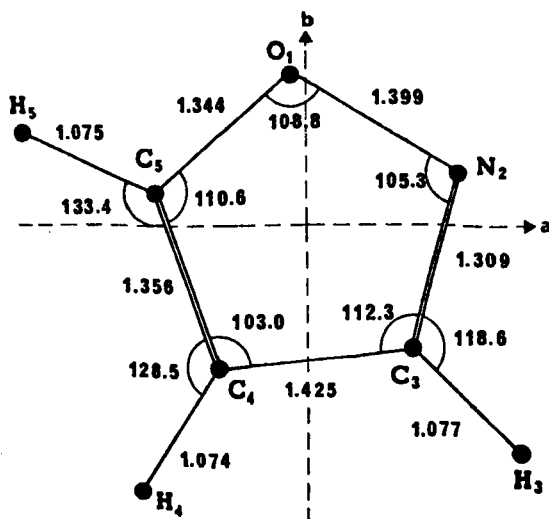


FIG. 1. Molecular dimensions of isoxazole (bond lengths in angstroms). Reproduced from Stiefvater²⁷⁴ by permission of the American Institute of Physics.

The dimensions thus established are generally similar to those determined by X-ray crystallography for several substituted isoxazoles (see, for example, Blanpain *et al.*^{276,277}). No significant distortion appears to occur on coordination with copper (I).¹³⁷

B. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Several studies of both the ¹H and ¹³C-NMR spectra of isoxazoles have been reported. For isoxazole itself the parameters are recorded in Table XI.^{278–283} An analysis of the ¹H-NMR spectrum of isoxazole in a liquid crystal solution also gave the dipole–dipole coupling constants: $D_{35} = -64 \pm 2$ Hz; $D_{45} = -300 \pm 2$ Hz; $D_{34} = -487 \pm 2$ Hz.²⁸¹

²⁷⁶ P. Blanpain and F. Durant, *Cryst. Struct. Commun.* **6**, 7 (1977); S. Biagini, M. Cannas, and S. Marongiu, *Acta Crystallogr., Sect. B* **25**, 2108 (1969); *J. Heterocycl. Chem.* **6**, 901 (1969).

²⁷⁷ L. Brehn, *Acta Crystallogr., Sect. B* **33**, 146 (1977).

²⁷⁸ S. D. Sokolov, I. M. Yuditseva, and P. V. Petrovskii, *Zh. Org. Khim.* **6**, 2584 (1970).

²⁷⁹ R. Huisgen and M. Christl, *Angew. Chem.* **79**, 471 (1967).

²⁸⁰ J. P. Kintzinger and J. M. Lehn, *Mol. Phys.* **14**, 133 (1968).

²⁸¹ B. M. Fung and M. J. Gerace, *J. Chem. Phys.* **53**, 1171 (1970).

²⁸² J. Gainer, G. A. Haworth, W. Hoyle, and S. M. Roberts, *Org. Magn. Reson.* **8**, 226 (1976).

²⁸³ K. Tori and T. Nakagawa, *J. Phys. Chem.* **68**, 3163 (1964).

TABLE XI
 NMR SPECTRA OF ISOXAZOLE

Parameter	Solvent	Reference
δ_{H^3} (ppm)	8.19	CCl ₄
	8.34, 8.44	CDCl ₃
	8.19	Liquid crystal
δ_{H^4} (ppm)	6.32	CCl ₄
	6.41, 6.53	CDCl ₃
	6.31	Liquid crystal
δ_{H^5} (ppm)	8.44	CCl ₄
	8.51, 8.64	CDCl ₃
	8.44	Liquid crystal
δ_{C^3} (ppm)	149.1	CHCl ₃
δ_{C^4} (ppm)	103.7	CHCl ₃
δ_{C^5} (ppm)	157.9	CHCl ₃
$J_{H^3-H^4}$ (Hz)	1.6	CCl ₄ , liquid crystal,
	1.7	Neat
$J_{H^4-H^5}$ (Hz)	1.6	CCl ₄ , liquid crystal,
	1.7	Neat
$J_{H^3-H^5}$ (Hz)	0	Liquid crystal
$J_{C^3-H^3}$ (Hz)	188.0	Neat
$J_{C^4-H^4}$ (Hz)	184.3	Neat
$J_{C^5-H^5}$ (Hz)	203.3	Neat

The ^{15}N -signal for isoxazole, 339.6 ppm downfield from aqueous tetramethylammonium chloride, is at much lower field than that for most other azoles,²⁸⁴ and is coupled to H-3, with $J_{\text{H-C-N}} = 14.4$ Hz.²⁸⁰

Empirical correlations have been made for the ^1H chemical shifts of various substituted isoxazoles.^{278,285} The structures of some fully substituted isoxazoles have also been determined by comparison of their ^{13}C -NMR spectra with those of model compounds.^{282,286}

C. PROTOTROPIC TAUTOMERISM OF ISOXAZOLE DERIVATIVES

Since the previous review¹ the tautomerism of compounds such as hydroxyisoxazoles/isoxazolones, along with that of other heterocyclic com-

²⁸⁴ M. Christl, J. P. Warren, B. L. Hawkins, and J. D. Roberts, *J. Am. Chem. Soc.* **95**, 4392 (1973).

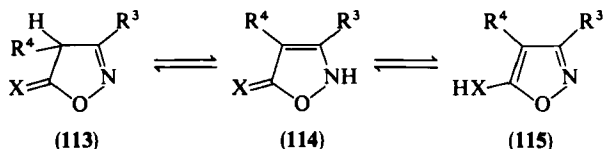
²⁸⁵ A. Battaglia, A. Dondoni and F. Taddei, *J. Heterocycl. Chem.* **7**, 721 (1970).

²⁸⁶ I. Yavari, S. Esfandiari, A. J. Mostashari, and P. W. W. Hunter, *J. Org. Chem.* **40**, 2880 (1975); G. M. Buchan and A. B. Turner, *J. Chem. Soc., Perkin Trans. 1* p. 2115 (1975).

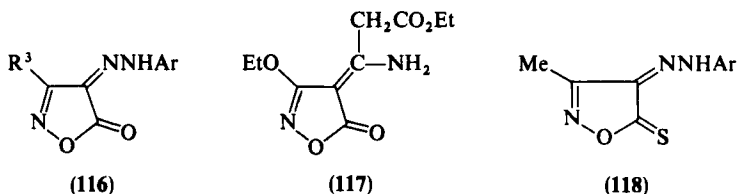
pounds, has been concisely surveyed²⁸⁷ and comprehensively reviewed.²⁸⁸ The generalizations which it is possible to make are summarized here, and an outline of very recent work is given.

1. 5-Substituted Isoxazoles

These derivatives can exist in three tautomeric forms, (113), (114), and



(115). For the compounds where X = O, the OH form (115) does not normally contribute significantly to the equilibrium mixture unless it is stabilized by, for example, hydrogen bonding to a 4-carbonyl substituent. The proportions of the CH (113) and NH (114) isoxazol-5-one forms are influenced by both medium and substituent effects. Mass spectroscopic studies provide some evidence for the CH form (113) in the vapor phase.^{212a} Appropriate 4-substituents can contribute further tautomerism. For example, there is evidence that 4-aryldio derivatives exist largely in the hydrazono form (116).²⁸⁸ Recently, X-ray crystallography revealed the structure (117) for the product of the reaction between ethyl 2-ethoxy-2-iminopropionate chloride and hydroxylamine.²⁸⁹



The sulfur derivatives (X = S) have been much less studied (cf. Elguero *et al.*,²⁸⁸ p. 391); they show a greater tendency toward the thiol form (115). A recent claim²⁹⁰ that some 4-aryldioisoxazole-5-thiones exist mainly in the CH form (cf. 113) has been disputed^{290a}; certainly the hydrazone form (118) seems by far more likely.

²⁸⁷ A. R. Katritzky, *Chimia* **24**, 134 (1970).

²⁸⁸ J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda "Advances in Heterocyclic Chemistry," Suppl. 1. Academic Press, New York, 1976.

²⁸⁹ P. Lugosi, G. Doleschall, L. Parkanyi, and A. Kalman, *Acta Chim. Acad. Sci. Hung.* **94**, 403 (1977).

²⁹⁰ N. A. Kassab, S. O. Abd Allah, and S. A. Elbahaii, *Z. Naturforsch., Teil B* **33**, 75 (1978).

^{290a} L. A. Summers, *Z. Naturforsch., Teil B* **33**, 1056 (1978).

The nitrogen derivatives ($X = \text{NH}$ or NR) almost invariably exist in the amino form (115).

2. 4-Substituted Isoxazoles

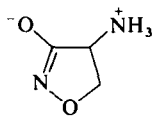
Simple 4-hydroxyisoxazoles and 4-aminoisoxazoles (the 4-mercapto compounds are so far unknown) normally exist in the XH form. Appropriate 4-substituents in compounds such as isoxazol-5-ones may however tautomerize as previously discussed.

3. 3-Substituted Isoxazoles

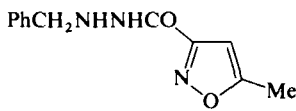
The situation for the 3-substituted compounds resembles that for the 4-substituted isoxazoles. The biologically important 4-aminoalkyl-3-hydroxyisoxazoles (see Section V) exist in the solid phase as zwitterions.²⁸⁸ A recent X-ray crystallographic study of 4-aminomethyl-3-hydroxy-5-methylisoxazole hemihydrate revealed "sandwiches" of sheets of zwitterions and water molecules held together by hydrogen bonding.²⁷⁷

V. Naturally Occurring and Biologically Active Isoxazoles

At the time of the earlier review many biologically active isoxazole and reduced isoxazole derivatives had been reported, including the naturally occurring antituberculosis antibiotic cycloserine (119), the monoamine oxidase inhibitor isocarboxazid (120), and isoxazolosteroids showing anabolic

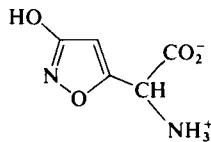


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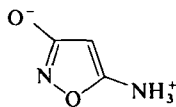


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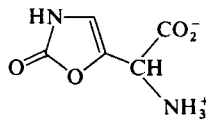
activity.¹ A further stimulus to work in this area was provided by the isolation of the CNS-active isoxazoles ibotenic acid (121) and muscimol (122), and the related oxazolone muscazone (123) from *Amanita muscaria* and



(121)



(122)



(123)

TABLE XII
BIOLOGICALLY ACTIVE ISOXAZOLES

Type of compound	Type of activity	Reference
Analog of muscimol	GABA agonist	293
Analog of ibotenic acid	CNA excitation	294
Substituted 3- and 5-arylisoaxazoles	Anthelmintic	8
5-(<i>o</i> -Chlorophenyl)-3-(4-pyridyl)isoaxazoles	Myolytic	112
3-Hydroxy-5-methylisoaxazole	Rice growth promotion	295
5-Arylisoxazolium salts ^a	Antibacterial	296

^a Activity correlated with substituent effects in aryl group.

other *Amanita* species.^{291,292} [Ibotenic acid is converted into muscimol by decarboxylation and into muscazone by irradiation (see Table VII).] As a result, very large numbers of biologically active isoxazoles have been reported, most of them in patents. These cannot be fully covered here, but the selection of recent reports listed in Table XII will illustrate some of the areas of interest.^{8,112,293-296} A recent paper describing the isolation of some isoxazolin-5-ones from legume seedlings suggests that natural products containing the isoxazole ring may occur more widely than had been supposed.²⁹⁷

²⁹¹ C. H. Eugster, *Prog. Chem. Org. Nat. Prod.* **27**, 261 (1969).

²⁹² R. G. Benedict, V. E. Tyler, and L. R. Brady, *Lloydia* **29**, 333 (1966).

²⁹³ P. Krogsgaard-Larsen, L. Natova, and S. B. Christensen, *Acta Chem. Scand., Ser. B* **31**, 577 and 584 (1977).

²⁹⁴ S. B. Christensen and P. Krogsgaard-Larsen, *Acta Chem. Scand., Ser. B* **32**, 27 (1978).

²⁹⁵ Y. Ota, *JARQ* **9**, 1 (1975); *Chem. Abstr.* **83**, 142844 (1975).

²⁹⁶ N. M. Omar and N. A. El-Rabbat, *J. Pharm. Sci.* **66**, 597 (1977).

²⁹⁷ F. Lambein, Y.-H. Kuo, and R. Van Parijs, *Heterocycles* **4**, 567 (1976).

Heteroaromatic Radicals, Part I: General Properties; Radicals with Group V Ring Heteroatoms

PETER HANSON

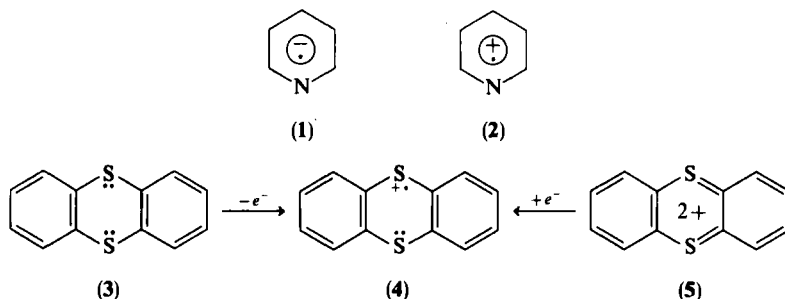
Department of Chemistry, University of York, Heslington, York, England

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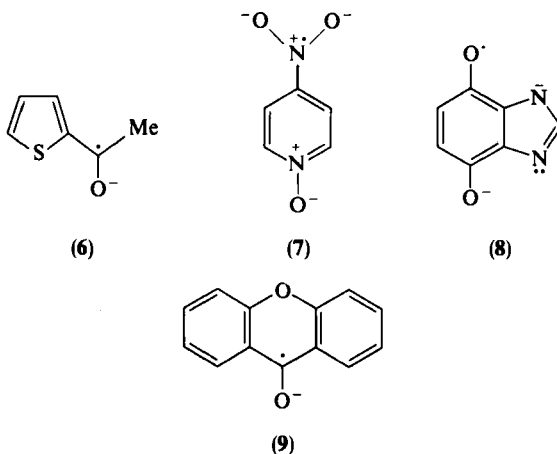
I. Introduction

A. DEFINITION OF TERMS AND SUBJECT MATTER

For the purpose of this review the term "heteroaromatic" is applied to π -radical species when they may be regarded as arising from aromatic heterocyclic molecules or ions by addition or removal of an odd number (usually one) of electrons. Thus, entities such as the anion- and cation-radicals of pyridine (1 and 2) are clearly heteroaromatic. The dilemma whether or not to regard thianthrene (3) as aromatic (its central ring possessing eight electrons) does not arise for the thianthrene cation radical (4): it is heteroaromatic on the grounds that it may formally arise by one-electron reduction of the aromatic thianthrenium dication (5).

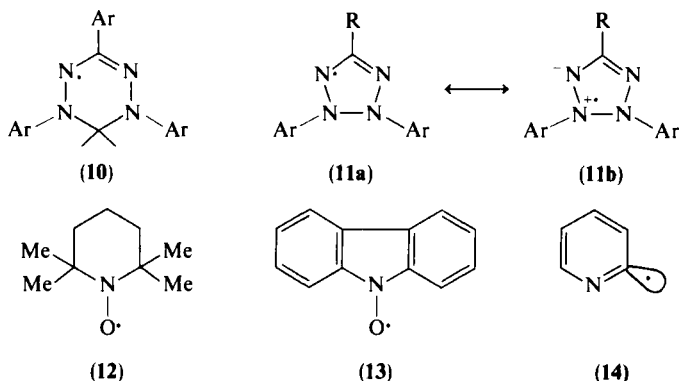


The definition also includes species in which a common radical function such as a ketyl, nitro anion-radical, or semiquinone is conjugated with a heteroaromatic system, e.g., 6–9. Certain major radical series are, however,



divided by the definition. Thus, verdazyls (10) are excluded as all the annular atoms do not participate in the conjugation, whereas the closely related tetrazolyl radicals (11) are considered aromatic. Similarly, while most ni-

troxyl (nitroxide) radicals, e.g., **12**, are excluded, the minority in which annular conjugation is present, e.g., **13**, are included. Since both verdazyls and nitroxyls have been extensively reviewed,¹⁻⁵ this arbitrary division constitutes no great disadvantage.



Aromatic heterocycles may, of course, give rise to σ -radicals, e.g., 2-pyridyl (**14**). This review does not treat of these except incidentally where there is ambiguity as to whether a radical is σ or π in character, or where a σ -radical occurs unexpectedly. Equally, transient radical adducts arising in homolytic substitution reactions which may contain a heteroaromatic moiety are not systematically considered. These have been discussed already in this Series.⁶

Finally, the solid-state behavior of heteroaromatic radicals is only incidentally mentioned, and species containing the porphyrin and similar systems are excluded on the grounds that they are more appropriately treated with their organometallic derivatives.

B. AIMS AND COVERAGE

The aim of the review is to describe the properties of heteroaromatic radicals in the qualitative language of organic chemistry and, in so doing, to provide a useful compendium of fact and references.

Different topics in the area to be discussed have been reviewed at various times previously. In general, therefore, emphasis is placed on the literature published since the previous appropriate review and usually derives from

¹ F. A. Neugebauer, *Angew. Chem., Int. Ed. Engl.* **12**, 455 (1973).

² E. G. Rozantsev and V. D. Sholle, *Russ. Chem. Rev. (Engl. Transl.)* **40**, 233 (1971).

³ A. R. Forrester, *Org. Chem., Ser. One* **10**, 139 (1973).

⁴ A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Chapter 5. Academic Press, New York, 1968.

⁵ S. F. Nelsen, in "Free Radicals" (J. K. Kochi, ed.), Vol. II, Chapter 21. Wiley (Interscience), New York, 1973.

⁶ F. Minisci and O. Porta, *Adv. Heterocycl. Chem.* **16**, 123 (1974).

that appearing in the past decade, although earlier work is cited as necessary. The review appears in two parts. Here, in Part One, the general properties of heteroaromatic radicals are discussed in terms of the distribution of spin; then the chemistry of heteroaromatic radicals containing solely Group V ring heteroatoms is reviewed. The literature is surveyed—it is hoped comprehensively—to the end of 1977, but citations from journals received at York in the first half of 1978 are included.

Reviews in related areas which bear on material of concern are listed at the outset.^{3-5,7-12}

C. CONVENTIONS AND ABBREVIATIONS

The representation of delocalized radical structures poses difficulties. As a general rule, in this chapter a heteroaromatic radical is represented by the relevant heterocycle with an inscribed circle containing a dot to denote the radical character and, if appropriate, a charge, e.g., **1** and **2**. Valence bond structures are used, when convenient, to assist in counting electrons, e.g., **3**, **4** and **5**, or when it is desired to indicate positions of high charge or spin population, e.g., **6-9**, or for clarity in expressing mechanism. Different valence bond structures for a particular entity are distinguished by **a**, **b**, **c**, etc. following its identifying number, e.g., **11a** and **b**. Nonradical aromatic molecules are represented by conventional Kekulé structures. Customary abbreviations are used for solvents: DME (dimethoxyethane), DMF (dimethylformamide), DMSO (dimethyl sulfoxide), HMPA (hexamethylphosphoramide), THF (tetrahydrofuran).

II. Unpaired Electrons and Radical Stability

A. SPIN DISTRIBUTION

In the majority of heteroaromatic radicals the unpaired electron is in a fully delocalized molecular π -orbital. The magnetic moment of the unpaired electron is quantized in an applied magnetic field, which fact gives rise to

⁷ G. Vincow, in "Radical Ions" (E. T. Kaiser and L. Kevan, eds.), pp. 151-209. Wiley (Interscience), New York, 1968; K. W. Bowers, *ibid.*, pp. 211-244; M. M. Urberg and E. T. Kaiser, *ibid.*, pp. 301-320.

⁸ M. Siskin, *Methods Free-Radical Chem.* **3**, 83 (1972).

⁹ A. Ledwith, *Acc. Chem. Res.* **5**, 133 (1972).

¹⁰ R. Zahradnik and P. Carsky, *Prog. Phys. Org. Chem.* **10**, 327 (1973).

¹¹ A. J. Bard, A. Ledwith, and H. J. Shine, *Adv. Phys. Org. Chem.* **13**, 156 (1976).

¹² N. Hirota, *Phys. Chem., Ser. Two* **4**, 85 (1975).

the possibility of observation of electron spin resonance (ESR) spectra. The interaction of the magnetic moment of the unpaired electron with the nuclear moments of those atoms in the radical which possess them may confer a fine structure upon an ESR spectrum whose character is governed by the nature of the nuclei involved and the degree to which they interact with the unpaired electron, at least in mobile liquid solution where anisotropic effects are averaged out. Various texts treat the theory and physical chemistry of the ESR phenomenon, and it is not intended to elaborate here other than to make a few assertions for future reference.¹³⁻¹⁶

First, the hyperfine splitting conferred on the ESR spectrum of a π -radical by interaction of the electron spin with a proton is proportional to the π -spin population ρ_i at the atom bearing the proton (the McConnell relationship).¹⁷ Thus, for a proton attached to carbon atom i the hyperfine splitting $a(\text{H})_i$ is given by Eq. (1), where Q_{CH} is the spin polarization parameter for the C—H bond.

$$a(\text{H})_i = Q_{\text{CH}}\sigma_i \quad (1)$$

Other than hydrogen, nitrogen is the only element commonly found in heteroaromatic compounds whose principal isotope (^{14}N) possesses a nuclear spin, and which consequently confers hyperfine splitting on the ESR spectra of derived α -radicals (i.e., radicals with π -spin population at N). The hyperfine splitting exhibited by nitrogen depends, however, not only on the π -spin population at nitrogen but also on that at adjacent atoms. Thus, the hyperfine splitting of a nitrogen atom is given generally by Eq. (2)

$$a(\text{N}) = Q_{\text{N}}\rho_{\text{N}} + \sum_j Q_{\text{XN}}\rho_{\text{X}} \quad (2)$$

where the Q parameters determine the relative importance of the spin population ρ_{N} at nitrogen and that ρ_{X} at the j adjacent atoms X. For example, the nitrogen splitting in a heteroaromatic radical such as **1** is given by Eq. (3), whereas that in a nitro anion-radical is given by Eq. (4):

$$a(\text{N})_{\text{pyr}} = Q_{\text{N}}\rho_{\text{N}} + 2Q_{\text{CN}}\rho_{\text{C}_{2,6}} \quad (3)$$

$$a(\text{N})_{\text{NO}_2} = Q_{\text{N}}\rho_{\text{N}} + Q_{\text{CN}}\rho_{\text{C}} + 2Q_{\text{ON}}\rho_{\text{O}} \quad (4)$$

In many examples it is found that the contribution to $a(\text{N})$ from adjacent carbon atoms is small: values of Q vary somewhat with the molecular orbital

¹³ A. Carrington and A. D. McLachlan, "Introduction to Magnetic Resonance." Harper, New York, 1967.

¹⁴ P. B. Ayscough, "Electron Spin Resonance in Chemistry." Methuen, London, 1967.

¹⁵ F. Gerson, "High Resolution E.S.R. Spectroscopy." Wiley, New York, 1970.

¹⁶ J. E. Wertz and J. R. Bolton, "Electron Spin Resonance: Elementary Theory and Practical Applications." McGraw-Hill, New York, 1972.

¹⁷ H. M. McConnell, *J. Chem. Phys.* **24**, 632 (1956).

(MO) method used to evaluate ρ s and with the type of species to which the expressions are applied, but it is usually found that $|Q_N| \approx 10 |Q_{CN}|$. (Their signs are probably opposed, Q_N being positive while Q_{CN} is negative on account of the σ - π spin polarization mechanism which confers parity on ρ). As a consequence, for the purpose of the qualitative arguments to be advanced later (see Section III,A,1, for example), Eq. (3) may be approximated to Eq. (5) for pyridine and comparable systems:

$$a(N) \approx Q_N \rho_N \quad (5)$$

Similarly Eq. (4) may be approximated to Eq. (6):

$$a(N)_{NO_2} \approx Q_N \rho_N + 2Q_{ON} \rho_O \quad (6)$$

In this instance Q_{ON} , although smaller in absolute magnitude than Q_N , is not negligible.¹⁵

The mathematical description of the spin distribution in an aromatic π -radical may be undertaken with varying degrees of sophistication depending upon the wave-mechanical method employed.¹⁸ The simplest is, of course, the Hückel MO method whose application to diamagnetic aromatic species underlies much of what organic chemists now take for granted. It may be applied valuably in understanding the general nature of the spin distribution in aromatic radicals (see Section II,B,1), but it fails in some respects. In particular, it fails to account for the experimental observation of hyperfine splittings from nuclei which occur at the nodes of Hückel MOs in the molecules of appropriate symmetry.

More sophisticated treatments overcome this by invoking a polarization by the unpaired electron of paired π -electrons. The consequence is the appearance of, usually low, negative values of spin population at those sites for which the Hückel method fails. Since the ESR experiment does not distinguish the sign of ρ , overall a better description of reality is obtained. Foremost in this respect has been McLachlan's method, and many assignments of hyperfine splittings in ESR spectra are based on the results of the McLachlan modification of a basic Hückel calculation when experimental data do not permit unambiguous assignment.¹⁹

Additional experiments may, of course, assist in assigning hyperfine splittings. For example, deuteration of specific sites in radicals modifies their ESR spectra considerably: ^2H has a nuclear spin of 1, and thus a doublet splitting arising from ^1H is replaced by a triplet splitting from ^2H ; since also the ratio of nuclear g -factors for the two isotopes $g_N(^2\text{H})$: $g_N(^1\text{H})$ is 0.1535,

¹⁸ J. N. Murrell and A. J. Harget, "Semi-empirical Self-Consistent Field Molecular Orbital Theory of Molecules." Wiley (Interscience), New York, 1972.

¹⁹ A. D. McLachlan, *Mol. Phys.* 3, 233 (1960).

the spectral line separation is smaller for the deuterated substance. The consequence is a considerable narrowing of the spectrum if a large ^1H splitting is replaced by a ^2H splitting. There may be an apparent simplification of the spectrum if a small ^1H splitting is replaced by a ^2H splitting, for this is then very small and unresolved. Methyl substitution and halogen substitution have both also been used in assigning spectra on the assumption that the influence of the substitution of the spin distribution is negligible.

Other experimental techniques of assistance in assigning ESR spectra involve nuclear magnetic resonance (NMR). The simplest is to record the NMR spectrum of the radical species, a method usually limited by the difficulty in attaining sufficiently high concentrations.²⁰ Another method makes use of the fact that the NMR signals of a substance are broadened in the presence of radicals derived from it and that the extent of individual signal broadening is related to the hyperfine splitting of the ESR spectrum. Thus, if the NMR spectrum has been assigned, a study of its broadening characteristics in the presence of small amounts of radicals can yield an assignment of the ESR spectrum.²¹ Electron nuclear double resonance (ENDOR) in solutions is a technique by which—at the price of more complicated technique and some sacrifice of sensitivity—the hyperfine splitting information contained in an ESR spectrum may be obtained in a simpler form; thus the solving of complex ESR spectra is obviated, and the assignment of ill-resolved ones facilitated.²²

Thus with, on the one hand, experimental results—especially from ESR spectroscopy—and on the other, if necessary, supplementary data from readily performed calculations, the organic chemist is well provided with information about the topology of the singly occupied MOs of radicals. The singly occupied MO of a radical is a *frontier orbital*: it is the occupied orbital likely to dominate the chemistry of the radical (see Section II,B); furthermore, if the reasonable approximation is made that the formation of a radical merely involves abstraction or addition of an electron from or to a diamagnetic molecule, without significant perturbation of its orbitals, then the spin distribution in the radical also gives information on the topology of the highest occupied molecular orbital (HOMO) (for a cation) or the lowest unoccupied molecular orbital (LUMO) (for an anion) of the parent neutral and diamagnetic molecule.

Use has been made of such considerations: Epiotis has accounted for the differential reactivity of chloronitrobenzenes toward nucleophiles in terms of the spin distribution in nitrobenzene anion-radicals; he has also correlated the reactivity of anisole and benzoate esters toward nucleophilic radicals

²⁰ K. H. Hausser, H. Brunner, and T. C. Jochims, *Mol. Phys.* **10**, 253 (1965).

²¹ C. S. Johnson and J. C. Tully, *J. Chem. Phys.* **40**, 1744 (1964).

²² K. Möbius and K. P. Dinse, *Chimia* **26**, 461 (1972).

with the spin distributions in the anion-radicals of anisole and benzaldehyde, respectively.²³ The regiospecificity of the various ring positions of a range of aromatic compounds, in reactivity with electrophiles, has been correlated with proton hyperfine splittings for those positions in appropriate radicals by Poole and Griffith and by Pedersen and co-workers.^{24,25} The latter include heterocycles and suggest that aromatic cation-radicals model the transition states for electrophilic substitution.

The quantitative correlation of the effects of substituents upon reactivity holds a venerable place in physical-organic chemistry. Substituent constants, such as Hammett's σ , measure the perturbation which a substituent makes on the electron distribution in a molecule; and the reaction constant ρ measures the consequence of this for a reactivity of interest. The correlation of ESR parameters by substituent constants holds promise, for it compares the empirical parameters with a real function of the very property they measure. Various endeavors have been made in this direction which are discussed in later Sections.

The present Section is closed in the hope that enough has been said to convince the reader that the spin distribution of an aromatic radical is an accessible quality which holds information for the organic chemist useful beyond merely describing the radical itself.

B. RADICAL STABILITY

For carbon-centered radicals, Griller and Ingold have clearly distinguished between thermodynamic and kinetic stability.²⁶ A radical which is thermodynamically more stable than another because of some structural feature, such as a greater extent of conjugation, is termed *stabilized*, whereas a radical which is long-lived, irrespective of its degree of stabilization, is termed *persistent*. This terminology will be adopted here, and the factors which influence both properties for heteroaromatic radicals will be discussed in this Section.

While it is conceptually useful to distinguish between stabilization and persistence, both qualities—like much else that is chemical—must ultimately be explicable in terms of the electron distributions within the radical. As for diamagnetic species, stabilization of a radical is associated with decrease in the *total* electronic energy; on the other hand, reactivity depends in large measure on the nature of the frontier orbitals of the radical, in particular

²³ N. D. Epiotis, *J. Am. Chem. Soc.* **95**, 3188 (1973).

²⁴ C. P. Poole and O. F. Griffith, *J. Phys. Chem.* **71**, 3672 (1967).

²⁵ E. B. Pedersen, T. E. Petersen, K. Torssell, and S. O. Lawesson, *Tetrahedron* **29**, 579 (1973).

²⁶ D. Griller and K. U. Ingold, *Acc. Chem. Res.* **9**, 13 (1976).

on their energies and coefficients at different atomic sites.²⁷ Reactions of radicals, especially self-reactions, are characteristically exothermic. By Hammond's postulate, the transition states for reaction are more representative of the reactants than of the products, whence the importance of the radical's frontier orbitals for their reactivity. It is intuitively acceptable that radicals should couple through positions of high spin population.

1. The Heteroatom

The common heteroatoms of heterocyclic molecules are more electronegative than carbon. Thus, for N and O, for which the sizes are comparable with C, an isoelectronic substitution of C should lead to a stabilization of the system. Figure 1 exemplifies this by comparing the simple Hückel MOs for

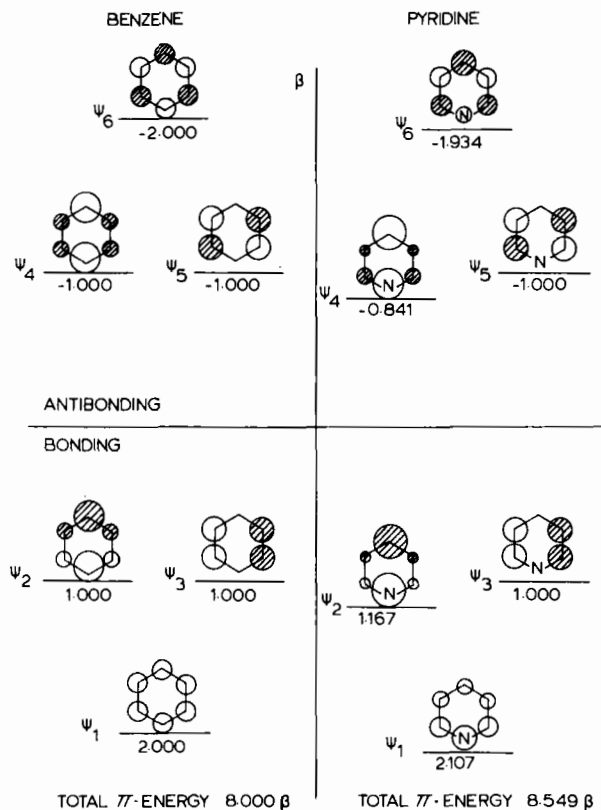


FIG. 1. A comparison of the Hückel MOs of benzene and pyridine. (Numerical data from Streitwieser *et al.*²⁸)

²⁷ I. Fleming, "Frontier Orbitals and Organic Chemical Reactions." Wiley (Interscience), New York, 1976.

pyridine and benzene. Compared with benzene, the orbitals ψ_1 , ψ_2 , ψ_4 , and ψ_6 in pyridine, all of which have electron density at the heteroatom, are individually stabilized, and the whole system of π -electrons is stabler by 0.549β .²⁸

The substitution also destroys the degeneracy in the frontier orbitals of benzene; thus, on formation of an anion-radical from pyridine, it is ψ_4 which receives the electron. As indicated in Fig. 1, the stabilized orbitals in pyridine are distorted from their symmetry in benzene. Thus, the coefficient of ψ_4 at the 2- and 6-positions is increased in pyridine, relative to benzene at the expense of the other positions, especially the 3- and 5-positions. The Hückel orbital coefficients c_i are related to spin population ρ_i by Eq. (7); thus, the simple Hückel model of the pyridine anion-radical predicts high spin population at positions 1, 2, 4, and 6, which is in good agreement with reality (see Section III,A,1), although the McLachlan procedure gives a rather more accurate quantitative description.^{15,29}

$$\rho_i = c_i^2 \quad (7)$$

Pyridine anion (**1**) is not persistent in solution: it dimerizes rapidly, mainly by coupling of the 4-positions which are the positions of highest spin population, consistent with what has gone before.³⁰

For the so-called π -excessive heterocycles, furan, pyrrole, and thiophene, where the heteroatom contributes two electrons to the aromatic sextet, the HOMO is of relatively high energy, compared to that in benzene, which fact confers the familiar high reactivity of these species toward electrophiles. Correspondingly, ionization to give cation-radicals is facile; however, such species are not persistent without stabilizing substitution or annelation (see Section III,D,3). Anion-radicals are also known, particularly for thiophene-containing systems (see Part Two; this Series, Volume 27, in press).

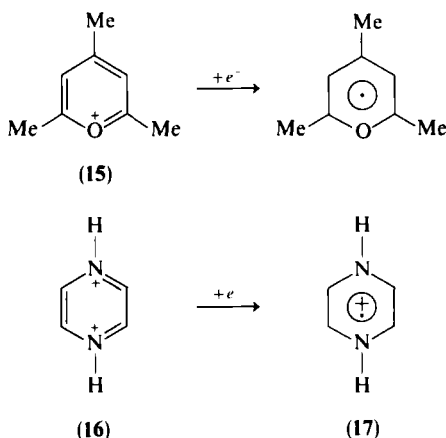
The size of sulfur and larger heteroatoms may result in less effective overlap of their orbitals with adjacent carbon atoms, which may offset any stabilization their electronegativity confers.

Heteroatoms also influence the charge carried by heteroaromatic radicals, just as they influence that of diamagnetic aromatic species. Thus, addition of an electron to the aromatic cations **15** and **16** yields radicals which are, respectively, neutral and cationic, albeit isoelectronic with benzene anion-radicals.

²⁸ A. Streitwieser, J. I. Brauman, and C. A. Coulson, "Supplemental Tables of Molecular Orbital Calculations," Vol 2, p. 246. Pergamon, Oxford, 1965.

²⁹ C. L. Talcott and R. J. Myers, *Mol. Phys.* **12**, 549 (1967).

³⁰ R. L. Ward, *J. Am. Chem. Soc.* **83**, 3623 (1961).



2. Conjugation

The extension of an aromatic π -system by, for example, benzo-annellation or coplanar phenyl substitution, stabilizes the system overall, raises the energy of the HOMO, and decreases that of the LUMO. The consequent decrease in ionization potential and increase in electron affinity imply the formation of cation-radicals for lower energy cost, and of anion-radicals with greater energy gain, the more extensive the π -system of the diamagnetic aromatic precursor.

This generalization will be qualified if the extension of conjugation includes heteroatoms. A pyrido-annellation, for example, should stabilize, overall, more than a benzo-annellation, but its influence on particular orbital energies will depend on the nodal properties of the MOs concerned in relation to the heteroatom. An orbital with a nonzero coefficient at the heteroatom will be stabilized, relative to the carbocyclic analog when the heteroatom is more electronegative than carbon and the substitution is isoelectronic; i.e., the heteroatom supplies the same number of electrons to the system as the atom it replaces (see Section II.B,1).

Clearly, the reactivities of radicals will be modified by conjugation changes which influence the energies of the singly occupied orbitals, but rather differently from the manner in which their diamagnetic precursors are influenced. For example, the increase in the energy of the HOMO on going from benzene to naphthalene increases the relative reactivity of naphthalene toward electrophiles. However, the radicals from these aromatic substances in which the corresponding orbitals are singly occupied, are *cation*-radicals, and for this reason reactivity toward electrophiles is less likely to be important.

Analogously, although the enhanced reactivity of quinoline derivatives (relative to pyridine counterparts) in nucleophilic additions such as the formation of pseudobases and Reissert compounds probably relates to the relatively lower energy of the LUMO in the quinoline derivatives, the radicals from these heterocycles, in which the corresponding orbitals are singly occupied, are *anionic*; thus, reactivity toward nucleophiles is also unlikely to be important.

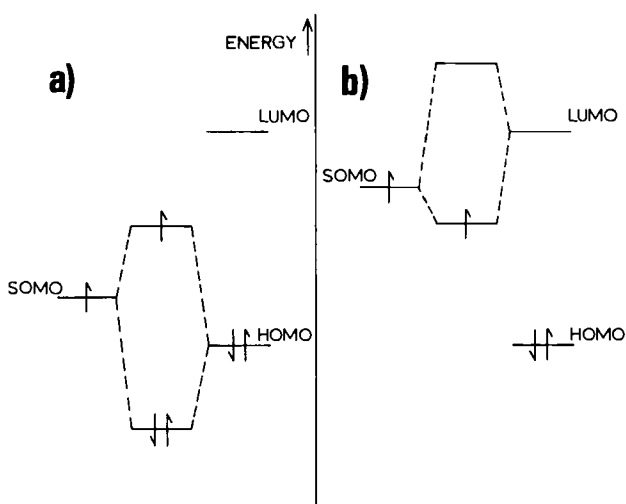
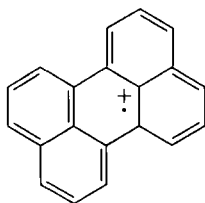


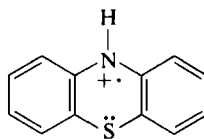
FIG. 2. (a) An electrophilic radical: predominant frontier orbital interaction involves the HOMO of the coreactant. (b) A nucleophilic radical: predominant frontier orbital interaction involves the LUMO of the coreactant.

However, charges aside, interaction of the singly occupied orbital of a radical with either the HOMO or the LUMO of a coreactant leads to a reduction in energy (see Fig. 2). Which interaction dominates the chemistry of the radical depends upon the relative energies of the orbitals concerned, the greater interaction occurring between orbitals the closer they are in energy, as indicated in Fig. 2.²⁷ The extent of conjugation in the radical, the heteroatoms it contains, and the charge it bears together determine whether a particular radical is electrophilic or nucleophilic, and the distribution of the singly occupied orbital determines the regiospecificity of its reactions. Thus, the thianthrene cation-radical (**4**) is found to be electrophilic, being readily attacked at S and position 2 by a range of nucleophiles; and the pyridine anion-radical (**1**) is found to be very strongly basic, undergoing protonation at N (see Section III,A,2 and Part Two).

Eberson and co-workers have recently discussed the probability that the interaction of ion-radicals with nucleophiles and electrophiles is subject to orbital symmetry constraints.^{31,32} This follows the observation that with perylene the cation-radical (**18**) the preferred course of reaction with halide ions is electron transfer rather than nucleophilic addition, whereas with the phenothiazine cation-radical (**19**) nucleophilic attack by Cl^- and Br^- occurs.



(18)



(19)

An orbital symmetry analysis showed that a transition state for nucleophilic addition formed from a $(4n + 1)$ cation-radical, e.g., **18**, and a halide ion would involve orbital interactions energetically unfavorable in symmetry terms and thus prejudice such a transition state in favor of electron transfer to which similar restrictions do not apply. On the other hand, **19** is isoelectronic with the anthracene anion-radical and is thus a $(4n + 3)$ species. The transition state for addition of halide becomes energetically favorable in symmetry terms in this instance.

Comparable arguments were advanced to account for the relatively slow rates of protonation observed for certain anion-radicals.³¹

Electron transfer between π -radicals constitutes their disproportionation. For cation- and anion-radicals, respectively, the disproportionation equilibria are given by Eqs. (8) and (9):



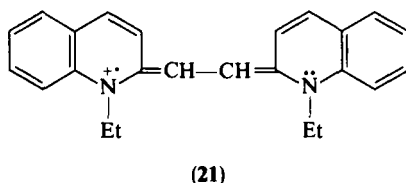
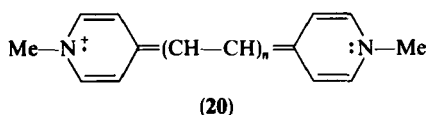
The free energy changes which govern these equilibria comprise enthalpic and entropic terms intrinsic both to the equilibrating species and to their solvation. Zahradnik and co-workers have sought to relate, for comparable systems where entropic and solvation effects are likely to be fairly constant, the position of the equilibrium to the difference in the π -energies of the equilibrating species.^{10,33} In evaluating the latter, the simple Hückel approximation is of no value, for in it the π -energy difference is zero. However, Zahradnik and co-workers made use of an earlier result of Hush and

³¹ L. Eberson, Z. Blum, B. Helgée, and K. Nyberg, *Tetrahedron* **34**, 731 (1978).

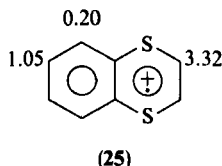
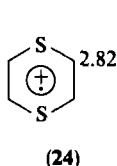
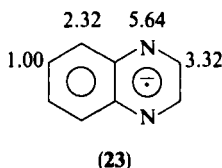
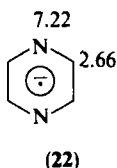
³² L. Eberson, *J. Chem. Soc., Chem. Commun.* p. 826 (1975).

³³ P. Carsky, S. Hünig, D. Scheutzwow, and R. Zahradnik, *Tetrahedron* **25**, 4781 (1969).

Blackledge that identifies the difference in π -energies with the Coulomb repulsion integral of the singly occupied orbital, calculated by the self-consistent field (SCF) MO method.³⁴ The nature of this integral is that it tends from positive values to zero as the extent of conjugation in the π -system increases, with the practical consequence that the more extensive the conjugated π -system in a radical, the less stable it is relative to its disproportionation products. This was demonstrated for a series of violene cation-radicals. For example, it is found that the disproportionation constants of the series of violenes (20) vary over nine orders of magnitude for $n = 0$ to $n = 5$ and that quinoline violenes, e.g., 21, disproportionate more readily than pyridine violenes with the same chain length.³³



A further significant consequence of variation in the extent of conjugation in aromatic radicals is demonstrated by a comparison of proton hyperfine splittings in pyrazine and quinoxaline anion-radicals (22, 23) and also in the cation-radical (24) of 1,4-dithiin and its benzo-counterpart 25.^{35,36} In each

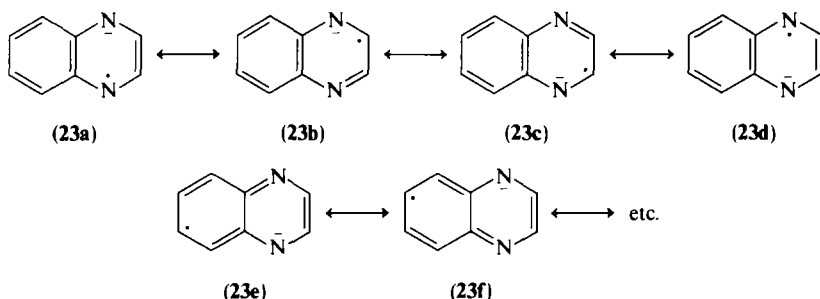


³⁴ N. S. Hush and J. Blackledge, *J. Chem. Phys.* **23**, 514 (1955).

³⁵ A. Carrington and J. dos Santos-Veiga, *Mol. Phys.* **5**, 21 (1962).

³⁶ P. D. Sullivan, *J. Am. Chem. Soc.* **90**, 3618 (1968).

of the bicyclic radicals the hyperfine splittings (in gauss) at the 2- and 3-positions is greater than that of the corresponding positions in the monocyclic radicals. Thus, although annelation results in a dispersal of the spin population—as witnessed by splittings from all the protons—it is uneven and the spin population at the 2- and 3-positions in the bicyclic radicals is actually augmented relative to their monocyclic counterparts. This demonstrates that greater stabilization is to be gained by electron pair delocalization than by single electron delocalization, as anticipated long ago by Dewar.³⁷ Valence bond structures most conveniently express the fact: the contributions of structures **23a–d**, where the “benzene” ring is intact, outweigh those (**23e, f** etc.) where it is sacrificed in order to delocalize the odd electron.

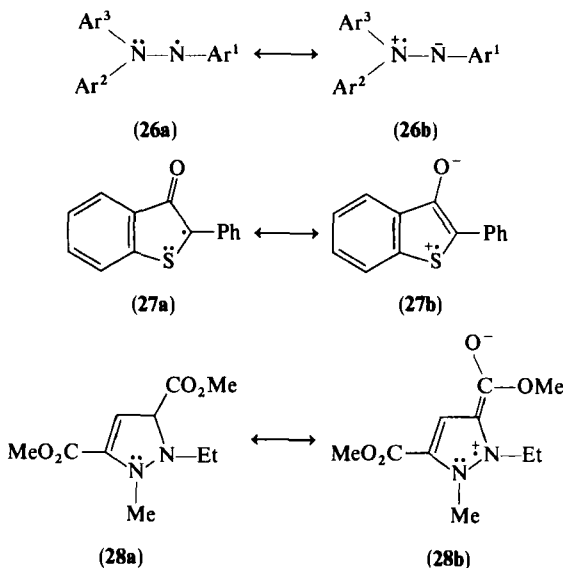


The stabilizing effect of electron pair delocalization underlies the mero-stabilization and “push–pull” mechanisms of radical stabilization suggested, respectively, by Katritzky and co-workers³⁸ and by Balaban.³⁹ Both of these ideas recognize that in neutral radical species canonical structures which may be drawn to delocalize the unpaired electron frequently require the separation of unlike charges. The weightings of such structures in the overall resonance hybrid will correspondingly be increased and the radical stabilized if functional groups are available to accommodate the charges. For example, in a triarylhydrazyl such as **26** delocalization of the unpaired electron onto the second nitrogen requires separation of charges in **26b**. The negative charge in **26b** on N-1 is accommodated by electron-withdrawing groups in Ar¹. The stability of diphenylpicrylhydrazyl (DPPH) testifies to the efficacy of this.³⁹

³⁷ M. J. S. Dewar, *J. Am. Chem. Soc.* **74**, 3353 (1952).

³⁸ R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. I* p. 1422 (1974).

³⁹ A. T. Balaban, *Rev. Roum. Chim.* **16**, 725 (1971).

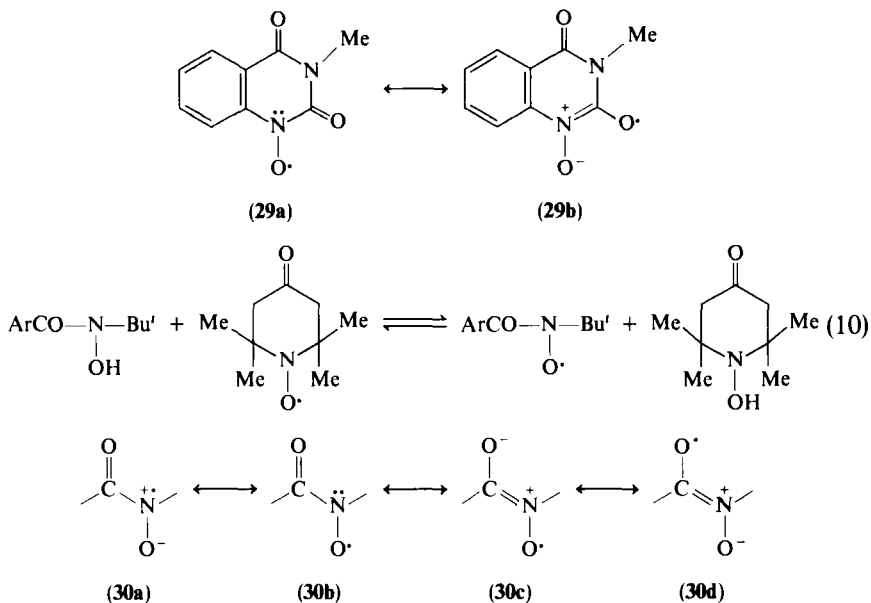


Katritzky and co-workers elaborated their version of the idea in heterocyclic forms and successfully predicted stability for radicals such as **27** and **28**.³⁸ However, in one example they suggested that a particular heterocyclic nitroxyl would be merostabilized by an adjacent keto function (**29**). This suggestion met criticism from Perkins and co-workers who studied the equilibria between an alkyl nitroxyl and various acyl nitroxyls and demonstrated the instability of the acyl nitroxyls relative to the alkyl reference compound (Eq. 10); furthermore, they showed that the relatively low value of nitrogen splittings in acylnitroxyls and the influence upon it of para-substituents in the aryl moiety could both be explained without postulating significant spin delocalization into the carbonyl group.^{40,41} The problem may be discussed in terms of the four partial structures **30a–d**. Structures **30a** and **30b** are those customarily drawn for nitroxyls; **30c** and **30d** are those whose relative importance is disputed. The proponents of merostabilization gave significant weighting to **30d**; Perkins' results imply **30c** to have the dominant weighting. In assessing the relative importance of structures **30c** and **30d**, it is worth bearing in mind the previously asserted points that electron pair delocalization is more gainful, energetically, than single electron delocalization and that (mero) stabilization results if dipolar charges are well accommodated. Comparing **30d** with **30a**, there is no difference in the charge distribution: merely the odd electron is redistributed. Comparing **30c** with

⁴⁰ T. C. Jenkins, M. J. Perkins, and N. P. Y. Siew, *J. Chem. Soc., Chem. Commun.* p. 880 (1975).

⁴¹ M. J. Perkins and P. Ward, *J. Chem. Soc., Chem. Commun.* p. 883 (1973).

30a, the separated charges are distributed in an alternative manner and hence, overall, stabilized. In addition, this is accomplished by paired electron delocalization (**30b** \leftrightarrow **30c**), whence it is expected that the significance of **30c** should outweigh that of **30d**. It is noteworthy that the contribution of **30c** localizes the unpaired electron, relatively, on the nitroxyl oxygen. Thus, another example indicates that stabilization of a radical may result in a local augmentation of spin population by comparison with a chosen reference, cf. **22** and **23**, **24** and **25**.

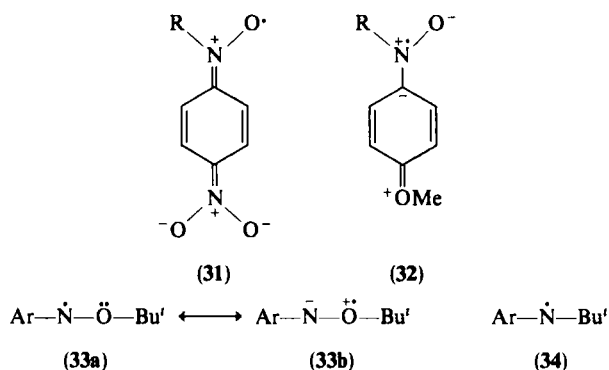


3. Substituent Effects

The foregoing bears closely on the electronic effects of substituents in radicals. Several years ago, Walter classified aromatic radicals into two main categories: *O* (opposite) and *S* (same), the terminology referring to the nature of the effects of substituents of different electronic character on a particular property of the radical.⁴² For example, if substituents of electron-donating and -attracting nature change a hyperfine splitting in opposite senses relative to the unsubstituted radical, the family of radicals is classified as *O* type. The basis for this behavior was suggested to be that type *O* radicals are structurally such that they may present either the unpaired electron or a lone pair for interaction with the substituent (cf. **26**). Both donor and acceptor groups can

⁴² R. I. Walter, *J. Am. Chem. Soc.* **88**, 1923 (1966).

delocalize the unpaired electron, but only acceptor groups can delocalize an electron pair. Since the latter is energetically preferable, pair delocalization predominates for acceptor substituents, and the two types of substituents have opposite effects overall. Radicals of *S* type were anticipated to be those of benzylic structures where substituents of both kinds may interact only with the unpaired electron. These suggestions were criticized by Janzen who felt that the evidence for an *S* category was, at the time, insubstantial, and that the substituents' role in *O* type radicals was not significantly to delocalize spin, but rather to influence the weightings of contributory forms by dipolar interactions.⁴³ Structures **31** and **32** show how acceptor and donor groups affect the nitrogen splitting in nitroxyl radicals: by interaction with the lone pair on N, acceptor groups decrease $a(\text{N})$, relative to that in the unsubstituted nitroxyl, by displacing spin from N to O. Donor groups, on the other hand, increase $a(\text{N})$ by localizing spin on N through stabilization of the dipolar charge.



Consistent with Janzen's suggestion, type *O* radicals have the substituent dependence of their hyperfine splittings correlated by substituent constants such as Hammett's σ .⁴³

Much of Janzen's criticism has been justified: the spin distribution in benzyl radicals themselves shows little substituent dependence⁴⁴; dimethylanilinium radicals, by Walter's structural criterion of type *S*, have proved to be of type *O*⁴⁵; the original data on triarylaminiun and triarylmethyl radicals, used to exemplify type *S*, have proved ambiguous⁴⁵⁻⁴⁷; authenticated *S* type behavior has been found only in a small group of acyclic aminyl

⁴³ E. G. Janzen, *Acc. Chem. Res.* **2**, 279 (1969).

⁴⁴ P. Neta and R. H. Schuler, *J. Phys. Chem.* **77**, 1368 (1973).

⁴⁵ B. M. Latta and R. W. Taft, *J. Am. Chem. Soc.* **89**, 5172 (1967).

⁴⁶ G. A. Pearson, M. Rocek, and R. I. Walter, *J. Phys. Chem.* **82**, 1185 (1978).

⁴⁷ H. Lankamp, W. T. Nauta, and C. MacLean, *Tetrahedron Lett.* p. 249 (1968).

radicals **33** and **34**.⁴⁸⁻⁵⁰ It appears, therefore, that for the majority of radicals the mechanism by which substituents have their influence on the distribution of spin is essentially by polar interactions which involve the substituents in electron pair displacements. This is true not only for charged species but also for many neutral species in which charge-separated structures contribute significantly to the resonance hybrid, e.g., nitroxyls^{43,51} and phenothiazin-10-yl radicals (see Part Two). Janzen's mechanism of substituent effects is precisely that which was termed merostabilization for other forms of structural variation, when the minor spin distributing structures are excluded from the latter, as discussed in the previous section.^{43,38}

Ingold emphasized the importance of the steric effects of substituents for the persistence of carbon-centered radicals, and Balaban for that of nitrogen-centered radicals.^{26,39} They are equally important for the persistence of heteroaromatic radicals, especially those with high spin populations at carbon and nitrogen. Thus, pyridine anion-radicals dimerize by coupling at position 4, as mentioned earlier.³⁰ This may be prevented by the introduction of sterically hindering methyl groups in positions 3 and 5 (see Section III,A,1). Similarly, carbazol-9-yl and phenothiazin-10-yl radicals may couple to give dimers containing N—C bonds (see Section III,D,3 and Part Two, respectively), but again these processes may be inhibited by alkyl substitution.

4. Conformation

Although simple aromatic systems are usually close to planar, conformational effects can occur when planar moieties are joined by a bond in which there is twist for steric reasons. There have been several studies of radicals derived from such systems, for there is interest in determining the effect of the twist on the spin distribution.⁵²⁻⁵⁷ With increasing twist the π - π conjugation between the two aromatic parts of the radical is increasingly

⁴⁸ S. F. Nelsen, R. T. Landis, L. H. Kiehle, and T. H. Leung, *J. Am. Chem. Soc.* **94**, 1610 (1972).

⁴⁹ W. C. Danen, C. T. West, and T. T. Kensler, *J. Am. Chem. Soc.* **95**, 5716 (1973).

⁵⁰ W. C. Danen and F. A. Neugebauer, *Angew. Chem., Int. Ed. Engl.* **14**, 783 (1975).

⁵¹ E. T. Strom, A. L. Bluhm, and J. Weinstein, *J. Org. Chem.* **32**, 3853 (1967).

⁵² L. O. Wheeler, K. S. V. Santhanam, and A. J. Bard, *J. Phys. Chem.* **70**, 404 (1966).

⁵³ L. O. Wheeler, K. S. V. Santhanam, and A. J. Bard, *J. Phys. Chem.* **71**, 2223 (1967).

⁵⁴ L. S. Marcoux, A. Lomax, and A. J. Bard, *J. Am. Chem. Soc.* **92**, 243 (1970).

⁵⁵ R. Biehl, K. P. Dinse, K. Möbius, and M. Plato, *Tetrahedron* **29**, 363 (1973).

⁵⁶ R. Biehl, K. Hinrichs, H. Kurrek, W. Lubitz, U. Mennenga, and K. Roth, *J. Am. Chem. Soc.* **99**, 4278 (1977).

⁵⁷ R. Hoffmann, R. Bissell, and D. G. Farnum, *J. Phys. Chem.* **73**, 1789 (1969).

disrupted and another spin transmission mechanism may become detectable.^{56,58,59} This is a π - σ polarization mechanism which can operate as σ -bonds of the one moiety eclipse the p-orbital of the atom of attachment of the other. For molecules of the shape of 9-phenylanthracene, modeled with bond lengths and angles equal to those in benzene, a van der Waals separation of the 1(8) and ortho protons imposes a dihedral angle of 65° between the planes of the two aromatic parts. This angle is close to the angle of twist which has to be allowed in MO calculations on such systems in order satisfactorily to reproduce the proton hyperfine splittings in the minor component.^{60,61} Results have been reported for the following heterocyclic systems: 9-phenylxanthenyl, 9-phenylthioxanthenyl, 9-phenylselenanthenyl neutral radicals, and 9-phenylacridine anion-radical.⁶¹⁻⁶⁵ Data for 10-arylphenothiazine and 10-arylphenoxazine cation-radicals are discussed in Part Two.

The dependence of the hyperfine splittings of alkyl groups upon their conformation in aliphatic radicals has been described.⁶⁶ The transmission of spin to β -protons is by a mainly hyperconjugative mechanism such that the β -H splitting is given by Eq. (11) where ρ_i is the π -spin population at the α -atom i to which the alkyl group is attached, θ is the dihedral angle between the $p_z(\pi)$ orbital of the α -atom i which contains the unpaired electron and the β -C-H bond, and B and B_0 are constants.¹⁵

$$a(\beta\text{-H}) = \rho_i B \cos^2 \theta + B_0 \quad (11)$$

For a variety of radicals B_0 is sufficiently small to be neglected to a first approximation.⁶⁷

When methyl groups are free to rotate, $\langle \cos^2 \theta \rangle = 0.5$, and all three protons couple equivalently. In this circumstance, Eq. (11) approximates to Eq. (12) which is comparable with the McConnell relationship, Eq. (1) (see Section II,A)

$$a(\text{Me}) \simeq 0.5B\rho_i = Q_{\text{Me}}\rho_i \quad (12)$$

⁵⁸ P. Neta and D. Meisel, *J. Phys. Chem.* **80**, 519 (1976).

⁵⁹ G. R. Underwood, V. L. Vogel, and J. A. Orio, *Mol. Phys.* **25**, 1093 (1973).

⁶⁰ Usually the resonance integral β^θ for a bond twisted through an angle θ is taken as $\beta^\theta = \beta^0 \cos \theta$, where β^0 is the resonance integral for the same bond without twist. [M. J. S. Dewar, *J. Am. Chem. Soc.* **74**, 3345 (1952).]

⁶¹ M. D. Sevilla and G. Vincow, *J. Phys. Chem.* **72**, 3641 (1968).

⁶² K. Maruyama, M. Yoshida, and K. Murakami, *Bull. Chem. Soc. Jpn.* **43**, 152 (1970).

⁶³ L. Lunazzi, A. Mangini, G. Placucci, and C. Vincenzi, *Mol. Phys.* **19**, 543 (1970).

⁶⁴ L. Lunazzi, A. Mangini, G. Placucci, and C. Vincenzi, *J. Chem. Soc., Perkin Trans. 1* p. 2418 (1972).

⁶⁵ A. Lomax, L. S. Marcoux, and A. J. Bard, *J. Phys. Chem.* **76**, 3958 (1972).

⁶⁶ D. H. Geske, *Prog. Phys. Org. Chem.* **4**, 125 (1967).

⁶⁷ R. O. C. Norman and B. C. Gilbert, *Adv. Phys. Org. Chem.* **5**, 53 (1967).

However, Q_{Me} (or B) may vary with type of radical, especially charge type, and also with the nature of the α -atom. Thus, methyl hyperfine splittings in alternant hydrocarbon anion- and cation-radicals, for which Hückel MO theory predicts identical spin populations at the methylated positions, typically differ by a factor of at least two.¹⁵

When rotation of an alkyl group RCH_2 is not free, two limiting cases may be distinguished: (1) truly locked conformation, or one "fixed" on the ESR time scale (i.e., where rotation takes place at a frequency less than ca. 10^6 Hz) and (2) a situation where, although rotation occurs rapidly, there are strongly preferred conformations. In the first case, the β -H splittings are weighted averages of the values of θ which correspond to the several conformations. The latter β -H splittings are temperature-dependent, a lowering of temperature resulting in the average β -H splitting tending toward that which corresponds to the lowest energy conformation.

Obviously, conformational effects which govern the extent of π -conjugation in a radical are of great import for stabilization and reactivity. Conformational effects in alkyl groups and similar addends are of less direct significance; nevertheless, knowledge that a particular alkyl group is not free to rotate may be of value in assessing steric effects which may be of primary importance to both stabilization and reactivity.

5. External Influences

Factors such as solvation and, in the case of ion-radicals, the counterion, may influence the properties of radicals. It is beyond the scope of this chapter to describe ion aggregation mechanisms and the factors which govern the hyperfine splittings manifested by counterions. The subject has been reviewed, however, by a prime mover in the field.¹² Suffice it to say that the association of an ion-radical with a counterion may lead to a considerable redistribution of spin within the radical with consequences for the chemistry. For example, disproportionation equilibria and persistence may be influenced by the nature of the association.⁶⁸ Closely allied to the phenomenon of ion association is, of course, solvation. Whether or not an ion-pair or other ionic assemblage exists in preference to free ions depends on the extent of the solvation of the ions. Nonionic radicals are also subject to variation in properties with change in solvent principally owing to interaction of the solvent with dipolar charges within the radical.

Dynamic processes concerning radicals are amenable to investigation by study of linewidth phenomena in ESR spectra. Essentially, as a radical

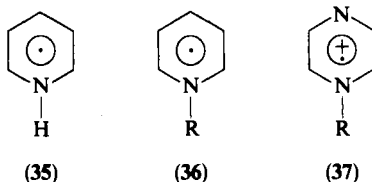
⁶⁸ J. Chaudhuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, *J. Am. Chem. Soc.* **90**, 6421 (1968).

undergoes dynamic changes such as might be associated with an association-dissociation equilibrium, a counterion exchanging sites within an ion-pair, conformational change, intermolecular ion-exchange processes, etc., hyperfine splittings are modulated with the consequence that lines in the spectrum are broadened. The relation of the extent of broadening to temperature or concentration changes which influence the dynamic process yields information on the dynamic processes themselves. This, too, has been reviewed for anion-radicals by Hirota.¹²

III. Radicals from Nitrogen Heterocycles

A. AZINE ANION-RADICALS AND ISOELECTRONIC SPECIES

This Section is concerned with the anion-radicals of the azines, e.g., **1** and **22**, their conjugate acids, e.g., **35** and **17**, and derivatives of the latter, e.g., **36** and **37**.



1. Anion-Radicals

a. Preparation. The electronegativity of the trigonal nitrogen atom(s) in azines confers an electron affinity which is high relative to that of analogous hydrocarbons and which facilitates the formation of their anion-radicals. This is often accomplished by exposure of a degassed solution of the azine in an inert solvent, commonly an ether, to an alkali-metal film or by electrochemical reduction in a polar solvent such as acetonitrile, dimethylformamide, or dimethyl sulfoxide, in the presence of an inert electrolyte.⁶⁹ Electron transfer from Me_3Si^- has also been used.⁷⁰ Frequently it is found that the anion-radicals exist as ion-pairs with the counterion when prepared in ethereal solvents. In many instances the radicals are persistent, if protected from air, but in others they rapidly dimerize. Thus, the first unequivocal observations of azine anion-radicals were made by Carrington and dos

⁶⁹ J. C. M. Henning, *J. Chem. Phys.* **44**, 2139 (1966).

⁷⁰ H. Sakurai, A. Okada, H. Umino, and M. Kira, *J. Am. Chem. Soc.* **95**, 955 (1973).

Santos-Veiga in 1962 upon pyrazine, quinoxaline, phenazine, and 1,4,5,8-tetraazanaphthalene.³⁵ They failed, however, to observe the anion of pyridine (1); in its stead they found that of 4,4'-bipyridyl: in ethereal solvents the ion-pairs of alkali metals and the pyridine anion-radical rapidly dimerize, yielding ultimately 4,4'-bipyridyl whose anion-radical is observed.^{30,35}

The anion-radical **1** was eventually observed, along with those of various of its derivatives, of pyrazine, and of pyrimidine, upon electroreduction in liquid ammonia.²⁹ This solvent was also used for reductions of azines by solvated electrons, formed upon dissolution of sodium metal.^{71,72}

b. Pyridine Anion-Radicals. i. Substituent effects on spin distribution. In Table I^{29,68,71-85} are presented experimental hyperfine splittings (in gauss) for substituted pyridine anions. The assignments are those of the original papers and may be based either upon experiment or upon calculation. Various points of interest arise from these data, the most obvious being that substituent effects in pyridine anions are complex. The simplest case is that of methyl substitution: it is seen that methyl groups in the 2- and 4-positions of the pyridine anion decrease the nitrogen splitting relative to that in the unsubstituted anion. This can be understood in terms of an increased weighting, relative to the parent anion, of structures, e.g., **38a-c**, which bear charge rather than spin on nitrogen: methyl groups, as electron-donating functions, repel the anionic charge from their points of attachment and it accumulates on the electronegative atom. Supporting this suggestion is the observation that, relative to the parent radical, the couplings of the 4- and 6-protons increase in the 2-methylated radical and those of the 2- and 6-protons increase in the 4-methylated radical.

⁷¹ A. R. Buick, T. J. Kemp, G. T. Neal, and T. J. Stone, *J. Chem. Soc. A* p. 666 (1969).

⁷² A. R. Buick, T. J. Kemp, G. T. Neal, and T. J. Stone, *J. Chem. Soc. A* p. 1609 (1969).

⁷³ N. M. Atherton, F. Gerson, and J. N. Murrell, *Mol. Phys.* **5**, 509 (1962).

⁷⁴ C. A. McDowell and K. F. G. Paulus, *Can. J. Chem.* **43**, 224 (1965).

⁷⁵ P. H. Rieger, I. Bernal, W. H. Reinmuth, and G. K. Fraenkel, *J. Am. Chem. Soc.* **85**, 683 (1963).

⁷⁶ M. T. Jones, *J. Am. Chem. Soc.* **88**, 5060 (1966).

⁷⁷ P. T. Cottrell and P. H. Rieger, *Mol. Phys.* **12**, 149 (1967).

⁷⁸ P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.* **37**, 2811 (1962).

⁷⁹ A. Gamba, V. Malatesta, G. Morosi, C. Oliva, and M. Simonetta, *J. Phys. Chem.* **77**, 2744 (1973).

⁸⁰ Y. Kawamura, K. Nishikida, and T. Kubota, *Bull. Chem. Soc. Jpn.* **46**, 737 (1973).

⁸¹ M. Itoh, T. Okamoto, and S. Nagakura, *Bull. Chem. Soc. Jpn.* **36**, 1665 (1963).

⁸² T. Kubota, Y. Oishi, K. Nishikida, and H. Miyazaki, *Bull. Chem. Soc. Jpn.* **43**, 1622 (1970).

⁸³ P. Cremaschi, A. Gamba, G. Morosi, C. Oliva, and M. Simonetta, *J. Chem. Soc., Faraday Trans. 2* **71**, 1829 (1975).

⁸⁴ P. Cremaschi, M. Morosi, C. Oliva, and M. Simonetta, *Gazz. Chim. Ital.* **105**, 509 (1975).

⁸⁵ A. R. Buick, T. J. Kemp, and T. J. Stone, *J. Phys. Chem.* **74**, 3439 (1970).

TABLE I
EXPERIMENTAL HYPERFINE SPLITTINGS (IN GAUSS) FOR PYRIDINE ANION-RADICALS

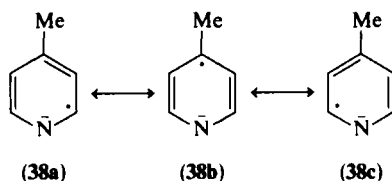
Substituent	1(N)	2	3	4	5	6	Counterion	System ^a	Reference
Unsubstituted	6.28 ± 0.03	3.14 ± 0.03	0.88 ± 0.03	9.10 ± 0.05	0.88 ± 0.03	3.14 ± 0.03		Na/HMPA	68
	6.28	3.55	0.82	9.70	0.82	3.55		E/NH ₃ (liq)	29
	6.31	3.55	0.79	9.63	0.79	3.55		Na/NH ₃ (liq)	72
2,3,4,5,6- ² H	6.38	0.50	0.13	1.49	0.13	0.50		Na/NH ₃ (liq)	72
2-Me	5.64	2.34	1.56	9.54	<0.10	4.39		Na/NH ₃ (liq)	72
3-Me	6.34	4.07	0.45	9.61	1.35	2.68		Na/NH ₃ (liq)	72
4-Me	5.67	3.80	0.60	11.38	0.60	3.80		E/NH ₃ (liq)	29
	5.67	3.68	0.58	11.31	0.58	3.68		Na/NH ₃ (liq)	72
2,3-di-Me	5.78	2.89	0.46	8.66	0.82	2.89		Na/NH ₃ (liq)	72
2,6-di-Me	4.86	3.16	0.71	9.29	0.71	3.16		Na/NH ₃ (liq)	72
3,5-di-Me	6.40	3.18	1.06	8.85	1.06	3.18		Na/NH ₃ (liq)	72
	6.21	3.41	0.80	8.96	0.80	3.41	0.39(Na)	Na/DME	73
	6.12	3.27	0.92	8.70	0.92	3.27	1.39(Na)	Na/DME	74
							0.47(Na)	Na/THF	
							0.14(K)	K/DME	
							0.15(K)	K/THF	
2-F	4.82	7.12	1.07	8.31	3.67	4.62		Na/NH ₃ (liq)	71
2-MeO	8.86	0.23	1.09	7.14	0.46	4.29		Na/NH ₃ (liq)	72
2,6-di-MeO	4.41	ca. 0.15	0.83	10.16	0.83	ca. 0.15		Na/NH ₃ (liq)	72
4-CN	5.67	1.40	2.62	2.33	2.62	1.40		E/DMF	75
2,3,5,6-tetra-CN	2.2	1.1	1.1	2.2	1.1	1.1		K/DME	76
								K/DME	76

2,3,4,5,6-penta-CN	2.65	1.15	1.15	ca. 0	1.15	1.15	K/DME	76
3-MeCO cis	1.15	2.6	6.29	4.73	1.30	7.89	E/DMSO	77
trans	1.46	4.80	5.99	3.38	1.08	7.73	E/DMSO	77
4-MeCO	4.36	0.05	2.96	5.59	3.39	0.18	E/DMF	78
2-NO ₂	1.893	8.184	2.728	0.591	3.777	0.866	E/MeCN	79
3-NO ₂	1.313	3.183	9.327	3.643	1.091	4.433	E/MeCN	79
	1.31	3.19	9.04	3.68	1.02	4.52	E/DMSO	77
4-NO ₂ ^b	2.473	0.451	3.033	7.817	3.033	0.451	E/MeCN	79
	2.48	0.50	3.16	8.43	3.16	0.50	0.180(K) K/DME	80 ^c
	2.55	3.00	0.53	8.72	0.53	3.00	K/DME	81
	2.622	0.398	3.021	7.257	3.021	0.398	E/DMF	82
	2.07	0.551	3.05	8.36	3.05	0.551	0.319(Li) Li/DME	83 ^c
2-Cl-5-NO ₂	1.41	0.22	1.11	3.52	8.51	3.52	E/DMSO	77
3,5-di-NO ₂	1.44	4.73	3.62	3.30	3.62	4.73	E/DMSO	77
	1.46	4.74	3.61	3.36	3.61	4.74	E/MeCN	84
2-CO ₂ ⁻	4.1	—	—	5.5	—	4.1	Na/NH ₃ (liq)	72
3-CO ₂ ⁻	1.64	1.09	—	7.28	0.47	8.83	Na/NH ₃ (liq)	72
4-CO ₂ ⁻	5.51	1.96	1.96	—	1.96	1.96	Na/NH ₃ (liq)	72
2-CH ₂ =CH	3.36	0.73(1H)	—	3.44	4.93	—	Na/NH ₃ (liq)	85
		7.72(2H)						
4-CH ₂ =CH	3.95	0.47	2.49	0.32(1H)	1.02	2.12	Na/NH ₃ (liq)	85
				8.30(2H)				

^a Reducing agent/solvent; *E* indicates electrochemical reduction.

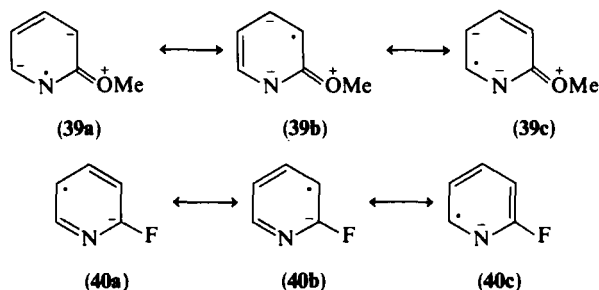
^b Assignment of 2- and 3-protons varies with MO method; McLachlan HMO result is tabulated.

^c Temperature variation of hyperfine splittings given in this reference.



The methyl splittings in the three monomethylated radicals fall in the order $4 > 2 > 3$, which is also the order of proton splittings in the parent radical. Clearly the positional dependence of the methyl splitting relates to the ability of the methyl group to interact with the singly occupied molecular orbital of the pyridine ring. It is this orbital's amplitude (strictly, its square in the Hückel approximation) at particular positions which largely determines the coupling of both the proton and the methyl group at these positions (see Fig. 1).

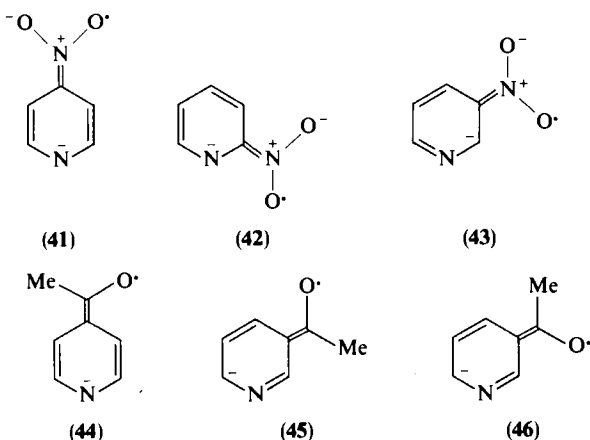
The influence of 2-methoxy and 2-fluoro substituents makes interesting comparison. Both substituents are mesomerically donating and inductively withdrawing, but their effects on the spin distribution are rather different. Relative to the parent anion, methoxy increases the splitting of the nitrogen atom and of the protons at the 3- and 6-positions and decreases those of the protons at the 4- and 5-positions; the fluoro substituent, on the other hand, decreases the nitrogen splitting with that of the 4-proton but increases the splittings of the protons at the 3-, 5-, and 6-positions. These redistributions of the spin are understandable in terms of the relative magnitudes of the mesomeric and inductive effects of the two substituents. Methoxy, for which the electron-donating mesomeric effect is dominant, repels the anionic charge, even from the adjacent ring-heteroatom (see structures 39a–c), while fluoro, for which the electron-attracting inductive effect predominates, has essentially the reverse effect (see structures 40a–c).



The behavior of pyridines with the mesomerically electron-withdrawing groups nitro, acetyl, and cyano is, by contrast with the foregoing, very different. In these radicals the substituent rather than the heterocycle becomes the primary site for unpaired electron density. For example, in the three mononitropyridine anions the heterocyclic nitrogen splitting is much

reduced relative to the parent, and a large substituent nitrogen splitting is observed. In addition, it is apparent that the substituent nitrogen splitting varies with position in the order $4 < 2 < 3$. Thus, although the spin distribution in the nitropyridine anion-radicals is quite different from that in the methylpyridine anion-radicals, the extent of interaction between the substituent and the heterocyclic ring positions falls in the same order ($4 > 2 > 3$) in both series and derives from the fact that the substituent interacts with the same MO (ψ_4 of Fig. 1) in each case. This contrasts with the benzene analogs where it is the actual substituent which determines whether ψ_4 or ψ_5 shall be the singly occupied MO.^{15,86} It is notable that the assignment of the two ring proton splittings in the 4-nitropyridine anion-radical depends upon the MO method used, thus implying ambiguity as to whether it is the substituent or the ring heteroatom which has the dominant role in determining that ψ_4 shall be stabilized relative to ψ_5 (Fig. 1).

Since the substituent splittings of the three mononitropyridine anion-radicals in acetonitrile are less than that for nitrobenzene anion-radical in the same solvent (10.32 G),⁸⁷ it might appear that the pyridine nucleus is more effective than the benzene nucleus at dispersing spin. However, on account of the preference for paired electron displacements (see Sections II,B,2,3), the relative reduction of the spin population at the substituent nitrogen in the heterocyclic anions, by comparison with nitrobenzene anion-radical, probably arises by increased contributions from structures which disperse *charge* into the ring rather than spin (see structures 41–43), but in doing so also reduce the spin density at nitrogen by displacing it onto oxygen. Since $|2Q_{ON}| < |Q_N|$ in Eq. (6), displacement of spin from N to O within the nitro group reduces $a(N)_{NO_2}$. Hückel–McLachlan calculations bear this out.^{79,87}

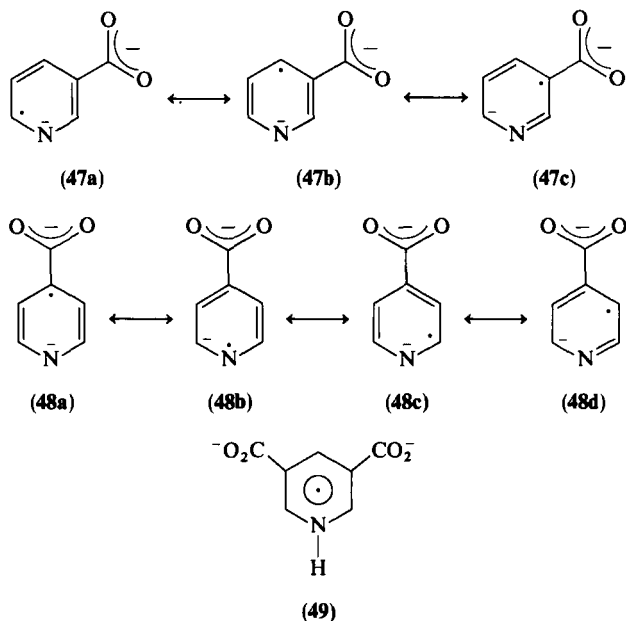


⁸⁶ See, for example, K. W. Bowers, in ref. 7.

⁸⁷ P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.* **39**, 609 (1963).

In common with other aromatic ketyls, the anion-radicals from the acetylpyridines show restricted rotation about the Ar—COMe bond, deriving from an increased bond order in the radicals, by comparison with their parent molecules.⁸⁸ This manifests itself in the 4-acetylpyridine anion-radical in the nonequivalence of the pairs of ortho and meta protons (**44**), while 3-acetylpyridine gives rise to two geometrically isomeric radicals, **45** and **46**.

Comparing the substituent acetyl methyl splittings with that of acetophenone anion-radical in DMF (6.825 G),⁸⁸ again the heterocyclic radicals show the smaller substituent splittings as in the case of the nitro anion-radicals. An exactly similar argument accounts for the facts: the greater capacity of the heterocyclic nucleus to accept charge results in a greater weighting for structures where spin is displaced from the ketyl carbon onto substituent oxygen and hence away from where it may couple with the methyl group. The large proton splittings for the terminal position of the side chain in the vinylpyridine anion-radicals and the large substituent nitrogen splitting for 4-cyanopyridine [$a(\text{N})_{\text{CN}} = 2.15$ G in benzonitrile anion radical⁸⁵] are further evidence of the distal localization of spin in the substituent as paired electron displacements take charge into the heterocycle.



⁸⁸ W. Kaminski, *Z. Naturforsch., Teil A* **25**, 639 (1970).

The data of Table I show that the carboxylate group (CO_2^-) has considerable influence on the spin distribution within the pyridine ring. For all three monosubstituted isomers the spin population at nitrogen is reduced by comparison with pyridine anion-radical itself. Again, this may be rationalized in terms of the interaction of charges within the species concerned. The substituent is itself anionic (the ESR spectra of the acids were obtained in liquid ammonia); thus, addition of an electron to the heterocycle forms *dianion* radicals. It is to be expected that the charges in such entities will be as widely separated as possible; hence dominant contributions to the hybrid forms of the radicals will be as in structures **47a–c** and **48a–d**. Inspection of these structures shows that the positions of high spin population, achieved by maximal charge separation, accord with those for which Table I indicates strongly coupled nuclei.

The radicals obtained upon reduction of pyridine dicarboxylic acids in liquid ammonia proved to have 1-hydropyridinyl structures, e.g., **49**.⁷² These are treated with similar species in Section III.A,2.

Attempts to obtain anion-radicals from a variety of chloro-, bromo-, and iodopyridines (and pyrimidines) resulted in formation of those of the parent heterocycles.⁷¹ Cleavage of carbon–halogen bonds on electron transfer to organic halides is a well documented phenomenon.⁸⁹ The C—Cl bond remains intact, however, in the anion-radical of 2-chloro-5-nitropyridine, no doubt because the odd electron is accommodated mainly in the nitro group.⁷⁷ In this context it is worth noting that the formation of anion radicals upon X irradiation of fluoropyridine in an adamantane matrix has recently been studied, with the finding that although 2-fluoro and 2,6-difluoropyridines gave π -anion-radicals, penta- and 2,3,4,6-tetrafluoropyridine gave σ -anion-radicals.⁹⁰ It seems the LUMO of the polyfluorinated pyridines is a σ^* -orbital which the substitution has stabilized relative to the π^* -orbitals. The suggestion is that the mesomeric electron donation by the fluorines destabilizes the π -orbitals while the cumulative inductive effect stabilizes the σ -orbitals, sufficient for crossover to occur. The rate of C—Cl bond fission in chlorostyrylpyridine anion-radicals has been studied kinetically by Alwair and Grimshaw, who have also studied related reactions of halogenated azanaphthalenes.^{91,92}

Hydroxypyridine anion-radicals have been observed isolated in an argon matrix.⁹³

⁸⁹ W. C. Danen, T. T. Kensler, J. G. Lawless, M. F. Marcus, and M. D. Hawley, *J. Phys. Chem.* **73**, 4389 (1969).

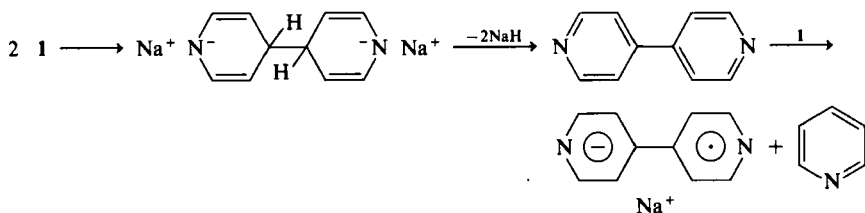
⁹⁰ M. B. Yim, S. DiGregorio, and D. E. Wood, *J. Am. Chem. Soc.* **99**, 4260 (1977).

⁹¹ K. Alwair and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 2* p. 1150 (1973).

⁹² K. Alwair and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 2* p. 1811 (1973).

⁹³ P. H. Kasai and D. McLeod, *J. Am. Chem. Soc.* **96**, 2342 (1974).

ii. Properties. The observation that reaction of pyridine with alkali metals leads to 4,4'-bipyridyl anion-radicals was first made by Ward, who proved the coupling position by means of experiments with deuterated substrate.³⁰ The reaction was developed synthetically by Luehder and co-workers, who prepared the products in quantity and performed magnetic susceptibility measurements on them.⁹⁴⁻⁹⁶ The mechanism of the coupling reaction was studied by Schmulback *et al.* who deduced a route to the observed product without requirement for excess of alkali metals or for hydrogen evolution (Scheme 1).⁹⁷ Rao and co-workers also studied the reaction spectroscopically,⁹⁸ and Dodd *et al.*⁹⁹ quoted electronic absorption characteristics for sodium-pyridine in THF together with sodium salts of the simple diazines.



SCHEME 1

The capacity for ion-pairing of pyridine anion-radicals has attracted interest. Thus, the methyl substituents in 3,5-lutidine impede its dimerization after the manner of pyridine, and its ion-pairing characteristics then become amenable to study.^{73,74}

Temperature variation of the ESR spectrum of 4-cyanopyridine was interpreted as arising from interconversion of two distinct species. From the nature of the activation parameters, different solvation patterns for the ion-pair were inferred to be the cause rather than any association-dissociation equilibrium of the radical.¹⁰⁰

The ion-pairs of nitropyridines continue to attract attention. Consistent with the substituent's being the primary residence for spin and charge in nitro anion-radicals, it was found that the counterion is associated with the oxygen atoms of the nitro group and lies on the C₂ axis of the radical.⁸⁰

⁹⁴ K. Luehder and G. Eckelmann, *Z. Chem.* **6**, 474 (1966); *Chem. Abstr.* **66**, 65370 (1967).

⁹⁵ S. Herzog and K. Luehder, *Z. Chem.* **6**, 476 (1966); *Chem. Abstr.* **66**, 121643 (1967).

⁹⁶ K. Luehder and I. Orfest, *Z. Chem.* **10**, 32 (1970); *Chem. Abstr.* **72**, 85746 (1970).

⁹⁷ C. D. Schmulback, C. C. Hinckley, and D. Wasmund, *J. Am. Chem. Soc.* **90**, 6600 (1968).

⁹⁸ V. Kalyanaraman, C. N. R. Rao, and M. V. George, *J. Chem. Soc. B* p. 2406 (1971).

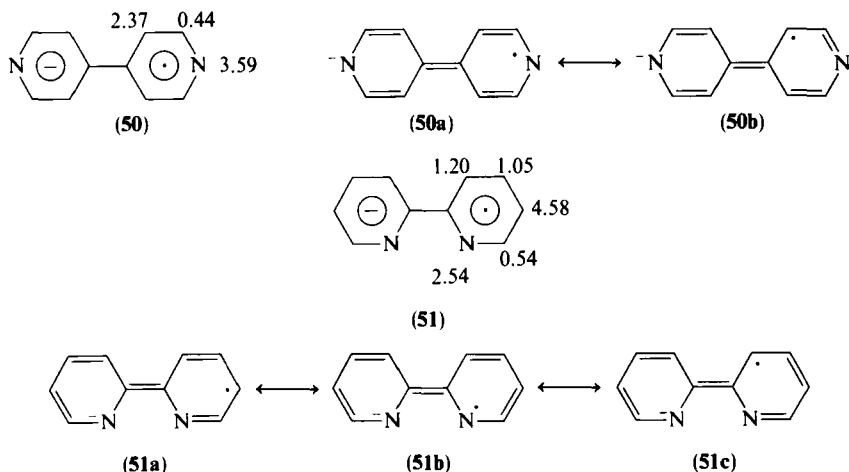
⁹⁹ J. W. Dodd, F. J. Hopton, and N. S. Hush, *Proc. Chem. Soc. London* p. 61 (1962).

¹⁰⁰ R. F. Adams, N. M. Atherton, A. E. Goggins, and C. M. Goold, *Chem. Phys. Lett.* **1**, 48 (1967).

Both Italian and Japanese schools have studied in detail the temperature dependence of the ion-pairing of 4-nitropyridine anion-radicals with alkali metals^{80,83}; unusual behavior has been noted for the ion-pairs with cesium and rubidium.¹⁰¹ The width of the ESR spectrum indicates that two nitropyridine moieties are involved, and dilution experiments imply their association to be of an electrostatic rather than covalent nature; but it is difficult to reconcile this with the lack of alkali-metal splitting.

Azine anion-radicals are highly basic and undergo N-protonation in the presence of proton sources. The resultant neutral 1-hydropyridinyl radicals are discussed subsequently (Section III,A,2).

c. Bipyridyl Anion-Radicals. As indicated already, the 4,4'-bipyridyl anion radical (**50**) was observed before that of pyridine itself. It was the first material for which the NMR line-broadening method was used to confirm the HMO assignment.^{30,35,102} 2,2-Bipyridyl also readily forms an anion-radical (**51**) which has elicited the greater interest on account of its characteristic ion-pairing properties: it coordinates the counterion between the two nitrogen atoms in the plane of the radical. The experimental hyperfine splittings of the two isomeric radicals are given in gauss in **50** and **51**.⁶⁹ A limited range of splittings in substituted 4,4'-bipyridyls has also been given.⁷²



The splittings indicate that there are large contributions to the structure which place the anionic charge in the one ring on the electronegative heteroatom and distribute the unpaired electron about the other (see structures **50a-b** and **51a-c**). In this respect, both bipyridyls behave in an analogous

¹⁰¹ A. Gamba, C. Oliva, and M. Simonetta, *Chem. Phys. Lett.* **36**, 88 (1975).

¹⁰² G. T. Jones and J. N. Murrell, *Chem. Commun.* p. 28 (1965).

manner to the nitro- and acetylpyridine anion-radicals discussed earlier except that now the heterocycle and the "substituent" become equivalent by symmetry. The behavior of the vinylog of **50**, 1,2-di(4-pyridyl)ethene, is entirely consistent.¹⁰³ There does not seem to have been any study of the unsymmetrical bipyridyl anion-radicals.

The propensity for ion-pair formation by 2,2'-bipyridyl anion-radicals was recognized in 1962.^{104,105} Activation parameters for electron exchange between the ion-pairs with K^+ and the free heterocycle were determined and the nature of ion triplets existing at low temperatures elucidated.^{106,107} Signs of alkali-metal hyperfine splittings were inferred and subsequently confirmed.^{108,109} A detailed analysis showed that the spin distribution in ion-pairs could be described using modified MO procedures with excellent results.¹¹⁰ The theoretical description of the ion-pairs continues to draw interest, however.^{111,112} In an elegant study Gooijer *et al.*¹¹³ compared the sodium ion-pairs of 2,2'-bipyridyl and 1,10-phenanthroline anion-radicals. Here, although structurally analogous, the organic radicals have singly occupied MOs of different symmetry, and conclusions were drawn regarding the nature of the ion-pairs and of the spin transmission to the counterion.

The chemical reactivity of 2,2'-bipyridyl anion-radicals has recently attracted attention: in a comparative study, again with 1,10-phenanthroline, the rates of exchange of ring protons for D at 100° were determined and related to their catalysis of equilibration of H_2-D_2 .¹¹⁴ Others have made a mechanistic study of the same reaction.¹¹⁵

d. Monocyclic Polyazine Anion-Radicals. Isotropic hyperfine splittings have been measured for a range of monocyclic polyazine anion radicals.^{29,30,35,69, 116–118} Representative values are indicated (in gauss) for **22**

¹⁰³ C. S. Johnson and R. Chang, *J. Chem. Phys.* **43**, 3183 (1965).

¹⁰⁴ E. Koenig and H. Fischer, *Z. Naturforsch., Teil A* **17**, 1063 (1962).

¹⁰⁵ A. Zahlan, F. W. Heineken, M. Bruin, and F. Bruin, *J. Chem. Phys.* **37**, 683 (1962).

¹⁰⁶ W. L. Reynolds, *J. Phys. Chem.* **67**, 2866 (1963).

¹⁰⁷ J. D. W. van Voorst, W. G. Zijlstra and R. Sitters, *Chem. Phys. Lett.* **1**, 321 (1967).

¹⁰⁸ T. Takeshita and N. Hirota, *Chem. Phys. Lett.* **4**, 369 (1969).

¹⁰⁹ T. Takeshita and N. Hirota, *J. Chem. Phys.* **58**, 3745 (1973).

¹¹⁰ T. Takeshita and N. Hirota, *J. Am. Chem. Soc.* **93**, 6421 (1971).

¹¹¹ K. Gustav, *Z. Chem.* **15**, 39 (1975); *Chem. Abstr.* **82**, 124524 (1975).

¹¹² K. Gustav, *Z. Chem.* **15**, 120 (1975); *Chem. Abstr.* **82**, 177774 (1975).

¹¹³ C. Gooijer, N. H. Velthorst, and C. MacLean, *Mol. Phys.* **24**, 1361 (1972).

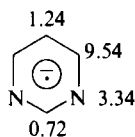
¹¹⁴ M. Ishizuka and A. Ozaki, *Nippon Kagaku Kaishi* p. 415 (1974); *Chem. Abstr.* **81**, 6551 (1974).

¹¹⁵ T. Nakamura, M. Soma, T. Onishi, and K. Tamaru, *Z. Phys. Chem.* **89**, 122 (1974).

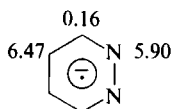
¹¹⁶ C. A. McDowell, K. F. Paulus, and J. R. Rowlands, *Proc. Chem. Soc., London* p. 60 (1962).

¹¹⁷ E. W. Stone and A. H. Maki, *J. Chem. Phys.* **39**, 1635 (1963).

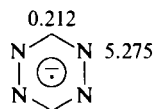
¹¹⁸ M. D. Sevilla, *J. Phys. Chem.* **74**, 805 (1970).



(52)



(53)



(54)

and **52**–**54**. Examination of these splittings shows that for **22** the singly occupied MO is similar to ψ_4 of benzene (see Fig. 1, and cf. **1**); however, for the remainder it is similar to ψ_5 (with very small, rather than zero, splittings occurring for two positions in 1,4-relationship). As in the case of pyridine, the degeneracy of the benzene LUMOs is destroyed by the heteroatomic substitution; and, of the two orbitals ψ_4 and ψ_5 , the most stabilized is that which has the largest coefficients at heteroatoms. The relative stabilization of ψ_4 in pyrazine and of ψ_5 in the rest then follows. For 1,3,5-triazine, for which no ESR spectrum has been recorded, despite attempts,^{35,117} the heteroatom substitution does not destroy the degeneracy of ψ_4 and ψ_5 .

Consequent upon the orbitals preferred for the unpaired electron, a high spin population occurs at C-4 in each of **1**, **52**, and **53**. These are the anion-radicals found to exhibit the least persistence.³⁵ Relative reactivities of the anion-radicals have been estimated by a cyclic voltammetric method as: **1** > 1,3,5-triazine anion-radical > **52** > **53** > **22** > **54**, which corresponds with qualitative observations on persistence and accords very closely with the ranking order of maximum spin populations at carbon.^{119,120} Dimerization of the radicals at positions of high spin population at carbon is proved for **1** and **52**, although the mechanism is by no means clear for **52** and other modes of reaction can also occur, e.g., proton abstraction from solvent or adventitious water.^{30,35,121–127}

The failure to observe ESR signals from the anion-radical of 1,3,5-triazine despite the polarographic evidence for its formation probably derives from a combination of factors: low concentrations due to its reactivity and broadened signals which occur when the unpaired electron occupies degenerate orbitals.¹²⁸

¹¹⁹ K. B. Wiberg and T. P. Lewis, *J. Am. Chem. Soc.* **92**, 7154 (1970).

¹²⁰ J. Komenda and A. Novak, *Scr. Fac. Sci. Nat. Univ. Purkyninae Brun.* **1**, 17 (1971); *Chem. Abstr.* **76**, 112509 (1972).

¹²¹ E. van't Land and D. van der Meer, *Rec. Trav. Chim. Pays-Bas* **92**, 409 (1973).

¹²² D. van der Meer, *Rec. Trav. Chim. Pays-Bas* **89**, 51 (1970).

¹²³ D. van der Meer, *Rec. Trav. Chim. Pays-Bas* **88**, 1361 (1969).

¹²⁴ D. van der Meer and D. Feil, *Recl. Trav. Chim. Pays-Bas* **87**, 746 (1968).

¹²⁵ J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.* **93**, 1871 (1971).

¹²⁶ J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.* **94**, 7941 (1972).

¹²⁷ P. J. Elving, S. J. Pace, and J. E. O'Reilly, *J. Am. Chem. Soc.* **95**, 647 (1973).

¹²⁸ J. R. Bolton, *Mol. Phys.* **6**, 219 (1963).

A limited number of simply substituted monocyclic polyazine anion-radicals have been studied. Thus, the 5-methylpyrimidine anion-radical has been shown to dimerize at the 2-position which is of low spin population.¹¹⁸ The substituent no doubt sterically inhibits the coupling at the 4-position which occurs for **52**,¹²¹ but the finding of an alternative coupling mode rather than persistence is somewhat surprising. The 5-nitropyrimidine anion-radical has been observed as a persistent species, but here the unpaired electron is largely located in the substituent.⁷⁷ The 2,2'-bipyrimidyl anion-radical (not a dimerization product) has also been observed.¹²⁹ The substitutions which convert pyrimidine into nucleic acid bases are not simple, but the derived anion-radicals meet the original definition of the term hetero-aromatic. They have been generated along with other species during pulse radiolysis of the bases.¹³⁰⁻¹³⁵ Nonaromatic radical adducts have been reported for these pyrimidines also.^{136,137} Radicals from pyrimidine bases have been trapped in solid matrices; the reader is referred elsewhere for reviews of this area.¹³⁸ Both 2-pyrimidone and 4,6-dimethyl-2-pyrimidone undergo one-electron electrochemical reduction followed by dimerization.^{139,140}

The observation of very small substituent splittings in a series of tetrazine anion-radicals (**55**), (R = Me, Et, *i*-Pr, cyclo-Pr, Ph₂CH, and Ph) confirms that the singly occupied orbital is as in **54**; the heterocycle, and not the nitrile groups, remains the primary site for the unpaired electron in **55** (R = CN).¹⁴¹⁻¹⁴⁴ By contrast, principal foci of spin density are outside the

¹²⁹ D. H. Geske and G. R. Padmanabhan, *J. Am. Chem. Soc.* **87**, 1651 (1965).

¹³⁰ P. S. Rao and E. Hayon, *J. Am. Chem. Soc.* **96**, 1295 (1974).

¹³¹ P. S. Rao and E. Hayon, *J. Am. Chem. Soc.* **97**, 2986 (1975).

¹³² E. Hayon, *J. Chem. Phys.* **51**, 4881 (1969).

¹³³ A. Grimison and M. K. Eberhardt, *J. Phys. Chem.* **77**, 1673 (1973).

¹³⁴ P. C. Shragge and J. W. Hunt, *Radiat. Res.* **60**, 233 (1974).

¹³⁵ G. A. Infante, E. J. Fendler, and J. H. Fendler, *Radiat. Res. Rev.* **4**, 301 (1973).

¹³⁶ J. K. Dohrmann and R. Livingston, *J. Am. Chem. Soc.* **93**, 5363 (1971).

¹³⁷ C. Nicolau, M. McMillan, and R. O. C. Norman, *Biochim. Biophys. Acta* **174**, 413 (1969).

¹³⁸ See, for example, T. J. Kemp, "Chemical Society Specialist Periodical Reports": Electron Spin Resonance **3** 221 (1976); **4** 163 (1977).

¹³⁹ B. Czochralska, D. Shugar, S. K. Arora, R. B. Bates, and R. S. Cutler, *J. Am. Chem. Soc.* **99**, 2583 (1977).

¹⁴⁰ B. Czochralska and D. Shugar, *Biochim Biophys. Acta* **281**, 1 (1972).

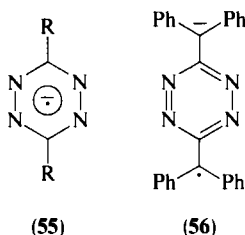
¹⁴¹ H. Malkus, M. A. Battiste, and R. M. White, *Chem. Commun.* p. 479 (1970).

¹⁴² A. Carrington, P. Todd, and J. dos Santos-Veiga, *Mol. Phys.* **6**, 101 (1963).

¹⁴³ G. A. Russell, R. Konaka, E. T. Strom, W. C. Danen, K.-Y. Chang, and G. Kaupp, *J. Am. Chem. Soc.* **90**, 4646 (1968).

¹⁴⁴ F. Gerson and W. Skorjanetz, *Helv. Chim. Acta* **52**, 169 (1969).

heterocycle in **56** as evidenced by the change in $a(\text{N})$ (from 5.07 to 1.62 G) on going from **55** ($\text{R} = \text{Ph}_2\text{CH}$) to **56**.¹⁴¹



The ESR spectrum from tricyano-1,3,5-triazine does not consist of the expected two sets of three equivalent nitrogen splittings, and it was suggested that a Jahn–Teller distortion removes the orbital degeneracy.¹⁴⁵ However, the MO parameters used to justify this have been criticized⁷⁶; those that had been successful in describing polycyanopyridine anion-radicals were employed instead and were found to indicate no stabilization of any orbital that would be sufficient to lift the degeneracy. An unspecified rearrangement of the radical was suggested, but the problem remains unresolved.

The influence of fluoro substitution on the reduction of a wide range of azines has been studied.¹⁴⁶

The ion-association phenomena manifested by pyrazine anion-radicals have been studied intensively since the first observation.³⁵ Simple ion-pairs form in ethereal solvents on treatment with alkali metals; various structures have been assigned which place the counterion adjacent to one heteroatom or symmetrically above the ring.^{76,116,147–154} Some recent work reinterprets aspects of the earlier material.^{155–157} Reduction of pyrazine and tetramethylpyrazine by alkali metals in ether solvents in the presence of the metal

¹⁴⁵ A. Carrington, H. C. Longuet-Higgins, and P. F. Todd, *Mol. Phys.* **9**, 211 (1965).

¹⁴⁶ D. M. W. van den Ham, G. F. S. Harrison, A. Spaans, and D. van der Meer, *Recl. Trav. Chim. Pays-Bas* **94**, 168 (1975).

¹⁴⁷ C. A. McDowell and K. F. G. Paulus, *Mol. Phys.* **7**, 541 (1964).

¹⁴⁸ N. M. Atherton and A. E. Goggins, *Trans. Faraday Soc.* **61**, 1399 (1965).

¹⁴⁹ N. M. Atherton and A. E. Goggins, *Trans. Faraday Soc.* **62**, 1702 (1966).

¹⁵⁰ N. M. Atherton, *Trans. Faraday Soc.* **62**, 1707 (1966).

¹⁵¹ J. dos Santos-Veiga and A. F. Neiva-Correia, *Mol. Phys.* **9**, 395 (1965).

¹⁵² T. A. Claxton and D. McWilliams, *Trans. Faraday Soc.* **65**, 3129 (1969).

¹⁵³ M. Brustolon, C. Corvaja, and L. Pasimeni, *J. Chem. Soc., Faraday Trans. 2* **68**, 2150 (1972).

¹⁵⁴ R. S. Hay and P. J. Pomery, *Aust. J. Chem.* **29**, 859 (1976).

¹⁵⁵ C. Gooijer and T. G. J. J. Blekemolen, *Chem. Phys. Lett.* **18**, 280 (1973).

¹⁵⁶ C. Gooijer and T. G. J. J. Blekemolen, *Chem. Phys. Lett.* **19**, 284 (1973).

¹⁵⁷ C. Gooijer and C. MacLean, *Mol. Phys.* **27**, 105 (1974).

tetraphenylboride yields triple ions of the type $[M_2\text{-pyrazine}]^+$. These have been studied by ESR.¹⁵⁸⁻¹⁶⁰ There is evidence for their participation at low temperatures in the usual reduction conditions also.^{161,162}

Reactions of pyrazine ion-pairs have been studied: dimerization and equilibration with anthracene.^{163,164} The ion-pair with Li features in the reaction of ethylene diamines with butyllithium to yield pyrazine derivatives.¹⁶⁵

Electronic absorption spectra have been reported for a variety of diazine anion-radicals in both liquid and solid solution.^{99,163,166} Polarographic reduction potentials have been measured for a wide range of azines and related to Hückel LUMO energies.¹⁶⁷

The calculation of polyazine radical parameters continues to attract the theoreticians.¹⁶⁸⁻¹⁷³

e. Polycyclic Azine Anion-Radicals. i. Azanaphthalenes. ESR spectra have been reported and analyzed by two sets of workers for the anion-radicals of quinoline and isoquinoline.^{68,174,175} The approaches of the two groups to the problem of assignment in these unsymmetrical radicals make interesting comparison. Their results are summarized in Table II. Both groups readily assigned the nitrogen splittings by recognition of the characteristic triplet pattern. The small differences in magnitude no doubt reflect solvent differences. The proton splittings surely also exhibit solvent

¹⁵⁸ S. A. Al-Badawi and T. E. Gough, *Can. J. Chem.* **48**, 2798 (1970).

¹⁵⁹ S. A. Al-Badawi and T. E. Gough, *Can. J. Chem.* **49**, 2059 (1971).

¹⁶⁰ T. E. Gough and R. G. Hacker, *J. Magn. Reson.* **6**, 129 (1972).

¹⁶¹ C. Gooijer, W. Oosterbeek, N. H. Velthorst, and C. MacLean, *Org. Magn. Reson.* **6**, 448 (1974).

¹⁶² C. Gooijer, D. M. de Leeuw, and C. MacLean *J. Magn. Reson.* **17**, 46 (1975).

¹⁶³ R. S. Hay and P. J. Pomery, *Aust. J. Chem.* **24**, 2287 (1971).

¹⁶⁴ R. S. Hay and P. J. Pomery, *Aust. J. Chem.* **25**, 2597 (1972).

¹⁶⁵ J. H. Wotiz, R. D. Kleopfer, P. M. Barelski, C. C. Hinkley, and D. F. Koster, *J. Org. Chem.* **37**, 1758 (1972).

¹⁶⁶ A. Grimison, G. A. Simpson, M. Trujillo Sánchez, and J. Jhaveri, *J. Phys. Chem.* **73**, 4064 (1969).

¹⁶⁷ S. Millefiori, *J. Heterocycl. Chem.* **7**, 145 (1970).

¹⁶⁸ P. J. Black and C. A. McDowell, *Mol. Phys.* **12**, 233 (1967).

¹⁶⁹ D. N. Nanda and P. T. Narasimhan, *Theor. Chim. Acta*, **32**, 321 (1974).

¹⁷⁰ V. Galasso, *Org. Magn. Reson.* **6**, 5 (1974).

¹⁷¹ G. M. Zhidomirov, I. A. Abronin, and N. D. Chuvylkin, *Zh. Strukt. Khim.* **16**, 162 (1975); *Chem. Abstr.* **82**, 155033 (1975).

¹⁷² G. D. Zeiss and M. A. Whitehead, *J. Chem. Soc., Faraday Trans. 2* **68**, 526 (1972).

¹⁷³ A. Hinchliffe, J. C. Cobb, and A. J. Duke, *Theor. Chim. Acta* **32**, 341 (1974).

¹⁷⁴ L. Lunazzi, A. Mangini, G. F. Pedulli, and F. Taddei, *J. Chem. Soc. B* p. 163 (1970).

¹⁷⁵ L. Lunazzi, A. Mangini, G. F. Pedulli, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna* **26**, 117 (1968).

TABLE II
ASSIGNMENT OF HYPERFINE SPLITTINGS (IN GAUSS) FOR QUINOLINE AND ISOQUINOLINE

	1	2	3	4	5	6	7	8	Solvent	Reference
Quinoline	3.95	3.29	1.26	7.80	3.90	1.14	2.02	3.46	HMPA	68
	3.85	4.40	0.86	8.44	4.06	0.73	2.40	2.73	DME	174
Isoquinoline	5.38	1.92	0.37	4.01	3.95	3.26	0.04	6.26	HMPA	68
	7.16	2.28	0.11	4.20	2.53	4.20	0.11	5.16	DME	174

effects, but, as Table II shows, the assignments disagree. Thus, while both groups are agreed that for quinoline the largest proton splitting is due to H(4) and the smallest three are H(7) > H(3) > H(6), their assignments for H(5), H(8), and H(2) differ. For isoquinoline, the ranking order of proton splittings also varies; both groups agree that H(1) and H(8) are greater than H(4), H(5), and H(6), but assignments within both these sets differ.

For quinoline, Szwarc's group based their assignments on supplementary experiments involving NMR line broadening and deuteration of the carbocyclic ring. This permitted unambiguous assignment of splittings to H(2), H(3), and H(4). The carbocyclic protons were then assigned on the basis of simple Hückel calculation. Isoquinoline was assigned on the basis of NMR line broadening and Hückel calculation only. The Italian group based their assignments on the spectral changes brought about by methylating each carbon atom in the substrates, together with ancillary McLachlan HMO calculations. They, too, felt their assignments for isoquinoline were unequivocal and used the experimental results to "test" the calculations for unsymmetrical radicals and to assist in the more difficult assignment of the quinoline spectra. Since, however, they had to define an empirical parameter to measure the perturbations of the spin distribution induced by methylation, and apply it somewhat arbitrarily when differences in splittings were of the same order of magnitude as the perturbation, it is probable that the American data are the more reliable. Doubt remains, however, since the different solvents could be responsible, at least in part, for the inconsistencies: Szwarc and co-workers found that the NMR spectrum of quinoline varied significantly with solvent, possibly the ESR spectra do also.

Others have also reported ESR work on quinoline and its methyl derivatives.¹⁷⁶

The ESR characteristics of quinoxaline and phthalazine anion-radicals have long been known.^{35,69,117} More recent work on quinoxaline and some methylated derivatives confirms the original assignment based on Hückel

¹⁷⁶ T. C. Christidis and F. W. Heineken, *Magn. Reson. Relat. Phenom. Proc. Congr. AMPERE*, 16th, 1970 p. 551 (1971); *Chem. Abstr.* **78**, 9850 (1973).

theory and disproves subsequent reassignments based upon more sophisticated calculations.^{35,69,167,177,178} Quinoxaline and phthalazine are also treated in work which reports ESR results for all six naphthyridine anion-radicals.^{179,180} ESR spectra have been reported for three tetraazanaphthalenes.¹⁸¹ Here the McLachlan HMO method is of limited success. The values predicted for proton splittings depend critically on the N—N bond integral. No single parametrization satisfactorily accounts for proton splittings in 1,4,5,8-, 2,3,6,7-, and 1,4,6,7-tetraazanaphthalene anion-radicals.

The reactivities of several azanaphthalene anion-radicals, after polarographic generation, are discussed by van der Meer.^{122,123} This includes the radicals of quinazoline and cinnoline whose ESR spectra do not appear to have been reported. The stability of carbon-halogen bonds in various azine anion-radicals, including quinoxaline and quinoline, has been discussed, as has the reactivity of quinoline anions toward alkyl halides.^{92,182} In the latter reaction alkylation occurs at the 1,2- and 2,4-positions. Heteroarylation of a range of electron-rich substrates by azine anion-radicals has been reported.¹⁸³ No mechanism is implied in the available abstract, but the apparent electrophilicity on the part of the azine anions is surprising.

ii. *Azaanthracenes and azaphenanthrenes.* Owing to ready dimerization, the anion-radical of acridine was not observed in early experiments.³⁵ However, it was subsequently observed both by metal reduction in DME and HMPA and by electrochemical reduction in pyridine and acetonitrile.^{68,184-186} Very comparable hyperfine splittings were observed in all the solvents with, in addition, sodium metal splittings in DME, indicative of the formation of a tight ion-pair.¹⁸⁶ A limited number of anion-radicals of substituted acridines has been described.^{186,187} Ultraviolet and visible spectra have been recorded and compared with that of anthracene.^{68,186}

The anion-radical of phenazine was described early, as also was that of 1,4,5,8-tetraazaanthracene.^{35,69,117}

No ESR data have been reported for anion-radicals of phenanthridines, but there is evidence for their polarographic formation and for the depen-

¹⁷⁷ J. A. Pedersen and L. T. Muus, *Mol. Phys.* **16**, 589 (1969).

¹⁷⁸ J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Am. Chem. Soc.* **90**, 4201 (1968).

¹⁷⁹ D. M. W. van den Ham, J. J. du Sart, and D. van der Meer, *Mol. Phys.* **21**, 989 (1971).

¹⁸⁰ P. Cavaliere d'Oro, R. Danieli, G. Maccagnani, G. F. Pedulli, and P. Palmieri, *Mol. Phys.* **20**, 365 (1971).

¹⁸¹ R. Danieli, L. Lunazzi, and G. Placucci, *J. Am. Chem. Soc.* **93**, 5850 (1971).

¹⁸² W. H. Smith and A. J. Bard, *J. Am. Chem. Soc.* **97**, 6491 (1975).

¹⁸³ A. K. Sheinkman, V. A. Ivanov, N. A. Klyuev, and G. A. Mal'tseva, *Zh. Org. Khim.* **9**, 2550 (1973); *Chem. Abstr.* **80**, 82601 (1974).

¹⁸⁴ H. G. Hoeve and W. A. Yeros, *Mol. Phys.* **12**, 597 (1967).

¹⁸⁵ S. Niizuma, M. Okuda, and M. Koizumi, *Bull. Chem. Soc. Jpn.* **41**, 795 (1968).

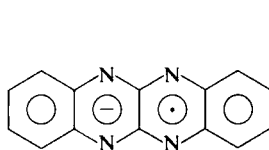
¹⁸⁶ S. Konishi, S. Niizuma, and M. Koizumi, *Bull. Chem. Soc. Jpn.* **43**, 3358 (1970).

¹⁸⁷ J. W. Happ and E. G. Janzen, *J. Org. Chem.* **35**, 96 (1970).

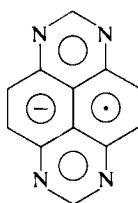
dence of the polarographic properties on molecular overcrowding.¹⁸⁸ By contrast, the symmetrical 9,10-diazaphenanthrene was investigated early, and the ESR results confirmed by subsequent observations^{68,129} No ESR signal was recorded for 1,10-phenanthroline by Stone and Maki using electrochemical reduction in DMSO; but in ethereal solvents, where ion-pairing is strong, signals are observed.^{113,117}

iii. *Tetraazaphenanthracene*. The radical-anion of 5,6,11,12-tetraazaphenanthracene (quinoxalino[2,3-*b*]quinoxaline) (**57**) has been recorded by Kuhn *et al.*¹⁸⁹ (see also Gerson's monograph,¹⁵ reference 166). The same radical had been prepared inadvertently by others and wrongly identified.^{129,190}

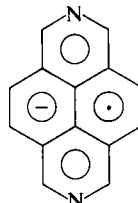
iv. *Azapyrenes*. ESR spectra have been analyzed by Gerson and co-workers for anion-radicals of 1,3,6,8-tetraazapyrene (pyrimido [4,5,6-*gh*]-perimidine (**58**) and 2,7-diazapyrene (benzo[*lmn*][3,8]phenanthroline) (**59**)^{191,192} (see also Section III,A,3d).



(57)



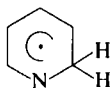
(58)



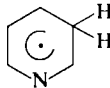
(59)

2. Neutral Radicals

a. *Nomenclature*. Neutral radicals e.g., **35**, are formed on protonation of azine anion-radicals. Nomenclature for such species is confused. Thus the terms "pyridinyl" "1-hydropyridinyl," "1-hydropyridine," "dihydropyridinyl," and "dihydropyridyl" have all been applied to **35** and its derivatives. The author strongly prefers "1-hydropyridinyl" on the grounds that the "-yl" ending implies a radical and the position of the hydrogen appended to the parent pyridine is indicated by the locant. The radical is thus distinguished from its isomers **60** and **61** whose derivatives are known and from σ -radicals such as 2-pyridyl (**14**).



(60)



(61)

¹⁸⁸ B. R. T. Keene and P. Tislington, *Recl. Trav. Chim. Pays-Bas* **84**, 488 (1965).

¹⁸⁹ R. Kuhn, P. Skrabal, and P. H. H. Fischer, *Tetrahedron* **24**, 1843 (1968).

¹⁹⁰ G. A. Russell and R. Konoka, *J. Org. Chem.* **32**, 234 (1967).

¹⁹¹ F. Gerson, *Helv. Chim. Acta* **47**, 1484 (1964).

¹⁹² J. Bruhin and F. Gerson, *Helv. Chem. Acta* **58**, 2422 (1975).

Although the terms "dihydropyridyl" and "dihydropyridinyl" are recent usage of the *Journal of the Chemical Society* (1977) and *Chemical Abstracts* (Collective Indexes 1972–1976), respectively, and their logic is apparent, the "di" prefix implies addition of a second hydrogen to pyridine whose position is unknowable. One is thus faced with the unfortunate *Chemical Abstracts* terminology "1,?-dihydropyridinyl" for a species whose structure is certain, or, omitting locants, with terminology which is ambiguous. Furthermore, in considering comparable species from diazines, there is need to distinguish clearly between, for example, the 1,4-dihydropyraziniumyl (cation) radical **17** and **62**. In the author's view, to name **62** as 1-hydropyrazinyl circumvents the confusion which would probably result from the use of a "dihydro" prefix.

b. 1-Hydropyridinyl Radicals. When the pyridine anion-radical was observed by reduction of pyridine with sodium in liquid ammonia, it was found that addition of ethanol to the solvent resulted in the formation of a new radical with a large proton splitting additional to the number found in the anion-radical. The radical was identified as 1-hydropyridinyl (**35**).⁷² Hitherto, this had been detected only in solid matrix or on pulse radiolysis.^{193,194} The ESR spectra of this species and several of its derivatives have been observed subsequently by both radiolytic and photolytic techniques. Thus, Neta radiolyzed aqueous solutions of pyridine and its derivatives containing an excess of *t*-butanol or formate.^{195,196} Under these conditions solvated electrons are the reactive entities which add to the pyridine substrates to yield anion-radicals which are rapidly protonated to give the 1-hydropyridinyl radicals (OH[•] radicals are intercepted by the added *t*-butanol or formate, and reactions of H atoms are inefficient). The p*K* of the ring NH group of **35** was found to be greater than 14.¹⁹⁶ Zeldes and Livingston and Dohrmann and co-workers have generated 1-hydropyridinyl radicals photolytically.^{197–205} The pyridine substrates, in solutions containing iso-

¹⁹³ C. Chachaty, *J. Chim. Phys.* **64**, 608 (1967).

¹⁹⁴ B. Cercek and M. Ebert, *Trans. Faraday Soc.* **63**, 1687 (1967).

¹⁹⁵ P. Neta, *Radiat. Res.* **52**, 471 (1972).

¹⁹⁶ R. W. Fessenden and P. Neta, *Chem. Phys. Lett.* **18**, 14 (1973).

¹⁹⁷ H. Zeldes and R. Livingston, *J. Phys. Chem.* **76**, 3348 (1972).

¹⁹⁸ H. Zeldes and R. Livingston, *J. Phys. Chem.* **77**, 2076 (1973).

¹⁹⁹ H. Zeldes and R. Livingston, *Radiat. Res.* **58**, 338 (1974).

²⁰⁰ H. Zeldes and R. Livingston, *Radiat. Res.* **62**, 28 (1975).

²⁰¹ H. Zeldes, R. Livingston, and J. S. Bernstein, *J. Magn. Reson.* **21**, 9 (1976).

²⁰² H. Zeldes and R. Livingston, *J. Magn. Reson.* **25**, 67 (1977).

²⁰³ T. Rakowsky and J. K. Dohrmann, *Ber. Bunsenges. Phys. Chem.* **79**, 18 (1975).

²⁰⁴ J. K. Dohrmann and R. Becker, *J. Magn. Reson.* **27**, 371 (1977).

^{204a} H. Zeldes and R. Livingston, *J. Magn. Reson.* **26**, 103 (1977).

²⁰⁵ J. K. Dohrmann and W. Kieslich, *J. Magn. Reson.*, **31**, 69 (1978).

propanol and acetone, were irradiated with UV light in the cavity of an ESR spectrometer. Two reaction mechanisms have been assumed: either the photoexcited pyridine abstracts H^\bullet from isopropanol, or the hydroxyisopropyl radical formed on photoreduction of triplet acetone reduces the aromatic compound. Japanese workers have brought about the photoreduction of pyridines in amines, and Minisci and co-workers have used both photoreduction and reduction by zinc metal of protiopyridinium ions.²⁰⁶⁻²⁰⁹

1-Hydropyridinyl radicals have given excellently resolved ESR spectra which have been assigned following MO calculations and partial deuteration experiments. Experimental results from various workers are compared in Table III for a series of C-monosubstituted 1-hydropyridinyl radicals.

There is a large measure of agreement between the results for **35**, particularly for the strongly coupled nuclei. It is clear that the singly occupied orbital corresponds to ψ_4 of pyridine (see Fig. 1) as in the case of the pyridine anion-radical (**1**). The nitrogen splittings exhibited by **1** and **35** are similar, but the ring proton splittings for the 2(6)- and 4-positions in **35** are larger than in **1**. This derives, in part, from the difference in electronegativity of the heteroatom in the two radicals and, in part, from the different Q values that the two radicals require. The determination of Q values appropriate to 1-hydropyridinyl radicals has been a major motivation for much of the work done.^{197,198,203,204} Comparison of the data of Tables I and III shows that, in general, substituents have the greater perturbing influence on the spin distribution in the anion-radicals in line with the arguments advanced over the nature of substituent effects in radicals in Section II,B,3.

There has been intensive study of 1-hydropyridinyl radicals bearing one or more carboxylic acid substituents.^{72,195,198-202} In basic solution these radicals are anionic, but the charge is associated with the ionization of the acid functions and not with the radical moiety. Equilibrium and kinetic data have been reported for the acid ionizations¹⁹⁸⁻²⁰² and the variation of persistence with structure discussed.¹⁹⁵

Hayon and co-workers have studied, by pulse radiolysis, 1-hydropyridinyl radicals ranging from those formed from simple C-acylpyridines to those from pyridoxine and pyridoxal phosphate.²¹⁰⁻²¹² Structural, spectroscopic, kinetic, and thermodynamic data have been presented. Various mechanisms have been adduced which involve **35** and analogous species from quinolines,

²⁰⁶ K. Kano and T. Matsuoka, *Tetrahedron Lett.* p. 1389 (1975).

²⁰⁷ K. Kano, T. Shibata, M. Kajiyara, and T. Matsuoka, *Tetrahedron Lett.* p. 3693 (1975).

²⁰⁸ L. Grossi, F. Minisci, and G. F. Pedulli, *J. Chem. Soc., Perkin Trans. 2* p. 943 (1977).

²⁰⁹ L. Grossi, F. Minisci, and G. F. Pedulli, *J. Chem. Soc., Perkin Trans. 2* p. 948 (1977).

²¹⁰ D. A. Nelson and E. Hayon, *J. Phys. Chem.* **76**, 3200 (1972).

²¹¹ W. Brühlmann and E. Hayon, *J. Am. Chem. Soc.* **96**, 6169 (1974).

²¹² P. N. Moorthy and E. Hayon, *J. Am. Chem. Soc.* **97**, 2048 (1975).

TABLE III
EXPERIMENTAL HYPERFINE SPLITTINGS (IN GAUSS) FOR MONOSUBSTITUTED 1-HYDROPYRIDINYL RADICALS^a

Substituent ^b	1(N)	1(H)	2	3	4	5	6	<i>g</i>	Solvent	Reference
Unsubstituted	5.79	4.21	5.79	0.74	11.62	0.74	5.79	—	NH ₃ (liq)/EtOH	72
	5.93	3.44	5.93	0.88	11.55	0.88	5.93	2.00292	H ₂ O, pH 12.1	195
	5.88	3.39	5.88	0.98	11.61	0.98	5.88	2.00290	2-propanol	197
	5.88	3.28	5.94	1.00	11.63	1.00	5.94	2.00294	acetone	197
	5.89	3.45	5.89	0.91	11.55	0.91	5.89	2.00296	H ₂ O	197
	5.89	3.47	5.89	0.96	11.63	0.96	5.89	2.00290	2-propanol	203
2-Me	5.29	2.68	4.97	0.56	11.64	1.37	6.61	2.00288	2-propanol	203
3-Me	5.86	3.42	6.18	1.13	11.28	0.74	5.43	2.00289	2-propanol	203
4-Me	5.58	2.53	6.01	1.19	12.31	1.19	6.01	2.00293	acetone	198
	5.57	2.69	5.98	1.16	12.32	1.16	5.98	2.00291	2-propanol	203
4-CH ₂ OH	5.65	3.46	5.67	0.84	6.37(2H)	0.84	5.67	2.00279	2-propanol/acetone	204
					0.19(1H)				(1:1)	
4-CHO	4.71	5.03	3.14	1.13	4.62	1.84	1.93	2.00379	2-propanol/acetone	204, 205
									(1:1)	
4-COMe	4.77	4.99	3.16	0.99	3.14	1.37	2.56	2.00370	2-propanol/acetone	205
									(1:1)	
2-CN	5.61	4.63	1.88	2.10	7.91	1.75	2.05	2.00287	2-propanol/acetone	204
									(1:1)	
3-CN	4.51	4.00	1.69	0.23	12.25	2.47	8.52	2.00290	2-propanol/acetone	204
									(1:1)	

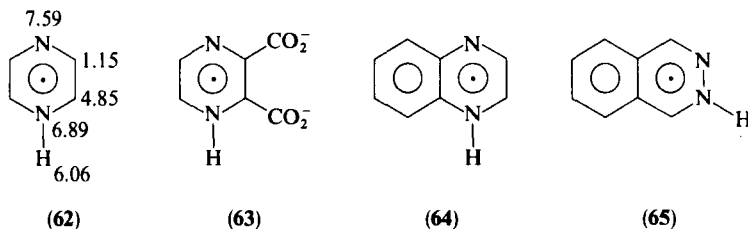
4-CN	5.40	5.09	4.03	0.46	2.12	0.46	4.03	2.00288	2-propanol/acetone (1:1)	204
	5.38	5.22	3.88	0.58	2.16	0.58	3.88	—	MeOH	208
3-CO ₂ H	3.53	3.48	1.40	—	11.82	1.94	9.54	2.00285	2-propanol/acetone (1:1)	204
	3.47	3.46	1.33	—	11.76	1.94	9.56	2.00297	acetone	204a
3-CO ₂ ⁻	4.46	3.82	2.45	—	11.81	1.65	8.47	2.00294	H ₂ O, pH 11.9	195
3-CONH ₂	4.26	3.75	1.77	—	11.76	2.22	8.55	2.00295	2-propanol/acetone (1:1)	204
	4.23	3.71	1.77	0.10(1H)	11.76	2.18	8.59	2.00297	acetone	204a
3-CO ₂ Me	3.46	3.48	1.30	0.26(3H)	11.82	1.93	9.59	2.00286	2-propanol/acetone (1:1)	204
	3.67	3.49	1.51	0.23(3H)	11.91	1.94	9.44	2.00296	acetone	204a
3-CO ₂ Et	3.50	3.47	1.36	0.23(2H)	11.83	1.94	9.55	2.00283	2-propanol/acetone (1:1)	204
4-CO ₂ H	5.19	5.28	3.31	1.03	0.51	1.03	3.39	2.00332	H ₂ O	198
	5.14	5.41	3.02	0.48	—	1.34	4.38	2.00325	H ₂ O, pH 4.6	195
4-CO ₂ ⁻	5.28	4.72	4.14	0.28	—	0.28	4.14	2.00326	H ₂ O	198
	5.26	4.95	3.90	0.53	—	0.53	3.90	2.00324	H ₂ O, pH 12.2	195
4-CO ₂ Et	5.19	5.09	3.60	0.75	0.90(2H)	0.75	3.68	2.00332	2-propanol/acetone (1:1)	204

^a Signs of hyperfine splittings given by some authors are omitted. Several of the assignments are tentative, especially for unsymmetrical radicals where splittings of comparable magnitudes occur.

^b Splittings due to nuclei in the substituent are given in the column appropriate to the substituted position.

isoquinoline, and acridines on photolysis of these heterocycles in methanol and other solvents.²¹³⁻²¹⁷

c. 1-Hydrodiazinyl Radicals. Attempts to prepare 1-hydrodiazinyl radicals from pyrazine, pyrimidine, and pyridazine, by photolysis in aqueous solutions containing isopropanol and acetone, led to paramagnetic products only in acidic conditions when the radicals formed were the corresponding *N,N'*-dihydrodiaziniumyl (cation) radicals.¹⁹⁷ Similar behavior was observed for photolysis in acidified methanol.²¹⁶ (See Section III,A,3.) However, photolysis of pyrazine in isopropanol containing acetone and a small quantity of aqueous sodium hydroxide led to the formation of the 1-hydro-pyrazinyl radical **62**. (The experimental hyperfine splittings indicated in **62** are in gauss.)²¹⁸



Consistent with the photolytic result, radiolysis of solutions of pyrazine gave only 1,4-dihydropyraziniumyl radical (**17**) in acidic or neutral conditions and no paramagnetic products in alkaline media.¹⁹⁶ However, pyrazine-2,3-dicarboxylic acid gave the 1-hydropyrazinyl-2,3-dicarboxylate (**63**) in strongly alkaline solution.¹⁹⁶

Using pulse radiolysis, Moorthy and Hayon have studied radicals from pyrazine, pyrimidine, pyridazine, quinoxaline, phthalazine, and acridine.²¹⁹ Electronic absorption characteristics and kinetic data were reported for the hydrodiazinyl neutral radicals, among others, and the *pK* values for their protonation to *N,N'*-dihydrodiaziniumyl radicals were given. The neutral

²¹³ A. Castellano, J. P. Catteau, and A. Lablache-Combier, *Tetrahedron* **31**, 2255 (1975).

^{213a} A. Castellano, J. P. Catteau, and A. Lablache-Combier, *J. Phys. Chem.* **80**, 2614 (1975).

²¹⁴ G. Vermeersch, N. Febvay-Garot, S. Caplain, and A. Lablache-Combier, *Tetrahedron* **31**, 867 (1975).

²¹⁵ A. Castellano, J. P. Catteau, A. Lablache-Combier, and G. Allan, *Can. J. Chem.* **51**, 3508 (1973).

²¹⁶ A. Castellano, J. P. Catteau, and A. Lablache-Combier, *J. Chem. Soc., Chem. Commun.* p. 1207 (1972).

²¹⁷ F. R. Stermitz, C. C. Wei, and C. M. O'Donnell, *J. Am. Chem. Soc.* **92**, 2745 (1970).

²¹⁸ H. Zeldes and R. Livingston, *Mol. Phys.* **27**, 261 (1974).

²¹⁹ P. N. Moorthy and E. Hayon, *J. Phys. Chem.* **78**, 2615 (1974).

radicals were found to react rapidly with oxygen although the nature of the reaction was unspecified.

Contrasting mechanisms for the photochemical formation of the isomeric hydrobenzodiazinyl radicals **64** and **65** have been elucidated.^{220,221}

d. 1-Substituted 1-Hydropyridinyl Radicals. Problems of nomenclature arise for N-substituted derivatives of **35** comparable with those which occur for **35** itself. Thus Kosower's radical **66** is termed 1-ethyl-1, 2-dihydro-4-(methoxycarbonyl)pyridyl and 1-ethyl-1,4-dihydro-4-(methoxycarbonyl)-pyridyl in recent *Chemical Abstracts* issues. The one, in the author's view, is undesirable; the other is inaccurate. For the purposes of this review, **66** will be termed 1-ethyl-4-methoxycarbonyl-1-hydropyridinyl and comparable nomenclature will be applied to its congeners.

1-Alkyl-1-hydropyridinyls were discussed by Forrester *et al.* in 1968 and again by Forrester in 1973.^{3,4} Nelsen also reviewed them in 1973.⁵

The finding, in 1964, that in the absence of air **66** is a persistent radical which may be isolated and distilled led to considerable work on this intriguing species and its analogs.²²²⁻²²⁴ Only recently, however, has a comparative account of the chemistry of the 1-methyl, 1-ethyl, 1-isopropyl, and 1-*t*-butyl homologs been published.²²⁵ By contrast, the necessity of the electron-withdrawing 4-substituent for the persistence of the radicals was recognized early; it was ascribed both to steric and to electronic effects.²²² The essential correctness of this conclusion has since been substantiated by studies of 1-alkyl-1-hydropyridinyls with different substitution patterns.²²⁶⁻²²⁸ Other mesomerically electron-withdrawing groups are effective in the 4-position; but, if the π -overlap between the substituent and the pyridinyl ring is sterically impeded by 3- and 5-alkyl groups, persistence is lost.²²⁶ An ester function in the 2- rather than the 4-position also confers a degree of persistence.²²⁷ Cyano groups in the 2- and 6-positions with steric blocking of the 4-position by alkyl substitution gives an indefinitely persistent radical.²²⁸

²²⁰ A. Castellano, J. P. Catteau, A. Lablache-Combier, and B. Plankaert, *Tetrahedron* **28**, 3511 (1972).

²²¹ A. Castellano, J. P. Catteau, A. Lablache-Combier, and B. Plankaert, *Tetrahedron Lett.* p. 4185 (1973).

²²² E. M. Kosower and E. J. Poziomek, *J. Am. Chem. Soc.* **86**, 5515 (1964).

²²³ E. M. Kosower and E. J. Poziomek, U.S. Patent 3,293,256 (1966); *Chem. Abstr.* **66**, 55399 (1967).

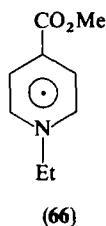
²²⁴ E. M. Kosower and H. P. Waits, *Org. Prep. Proced. Int.* **3**, 261 (1971).

²²⁵ E. M. Kosower, H. P. Waits, A. Teuerstein, and L. C. Butler, *J. Org. Chem.* **43**, 800 (1978).

²²⁶ M. Itoh and S. Nagakura, *Bull. Chem. Soc. Jpn.* **39**, 369 (1966).

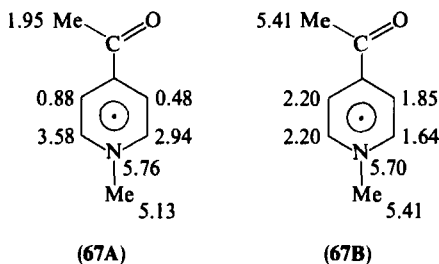
²²⁷ H. Watanabe, Y. Ikegami, and S. Seto, *Chem. Lett.* p. 1107 (1972).

²²⁸ A. R. Katritzky and F. Soti, *J. Chem. Soc., Perkin Trans. 1* p. 1427 (1974).



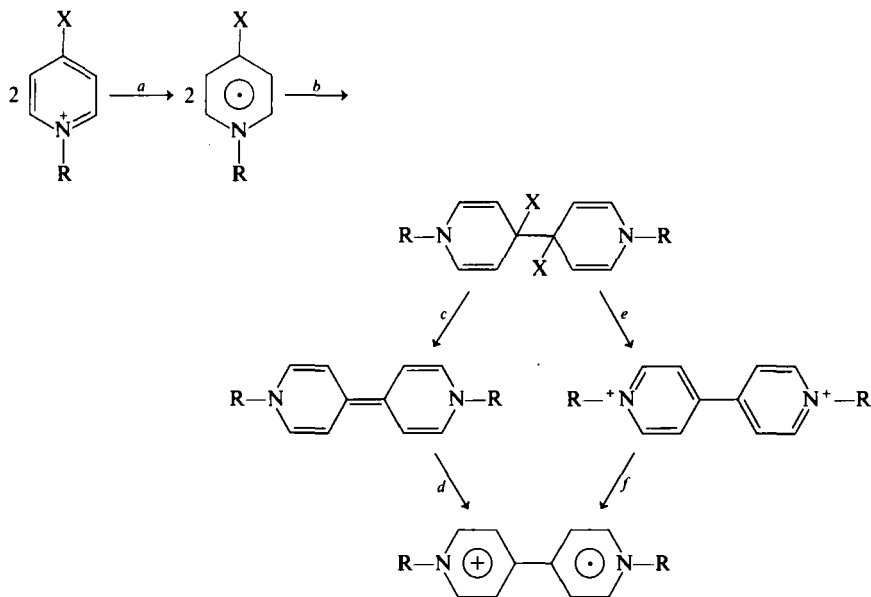
Synthesis of 1-alkyl-1-hydropyridinyls is by reduction of the corresponding pyridinium ion. On a preparative scale this has been effected using either zinc or sodium amalgam, with acetonitrile as solvent, in stringently oxygen-free conditions.²²²⁻²²⁴ For ESR measurements, zinc or potassium reduction in a range of solvents has been used; treatment merely by base in an alcohol or dimethyl sulfoxide is also often effective.²⁰⁸ (The mechanism of reduction of this type of system has been discussed.¹⁴³) Photoreduction has also been used.²⁰⁹

ESR spectra have been published for this family of radicals since their discovery^{222,225-228}; recently, however, a reinterpretation of results for 4-acetyl-1-methyl-1-hydropyridinyl has been presented.²⁰⁸ Minisci and co-workers found implausible the proposed structure of a radical obtained by alkali treatment of 4-acetyl-1-methylpyridinium salts.^{208,229} In the course of reinvestigation it was discovered that the spin distribution in 4-acetyl-1-methyl-1-hydropyridinyl is uniquely susceptible to solvent effects as shown in **67A** and **67B** in which the splittings indicated (in gauss) correspond to solutions in THF and water, respectively. A marked dependence on solvent polarity of the weightings of dipolar canonical structures was suggested in explanation.²⁰⁸ A similar, though lesser, degree of solvent dependence has also been reported for splittings in the *N*-H analog of this radical (i.e., without the nitrogen substituent) and has been reproduced in MO calculation by varying the Coulomb integral of the acetyl oxygen.²⁰⁵



²²⁹ M. Frangopol, P. T. Frangopol, C. L. Trichilo, F. E. Geiger and N. Filipescu, *J. Org. Chem.* **38**, 2355 (1973).

In the absence of a 4-substituent, 1-alkyl-1-hydropyridinyl radicals dimerize rapidly. Simple 1-alkyl-1-hydropyridinyls, generated electrochemically from the corresponding pyridinium salts, form 1,1'-dialkyl-1,1',4,4'-tetrahydro-4,4'-bipyridines which are oxidized at the prevailing potential to dialkylviologen cation-radicals which form the final product (Scheme 2; X = H, route *abcd*).²³⁰



SCHEME 2

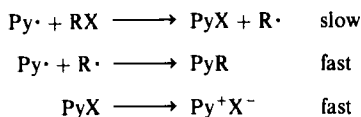
Dimerization may also occur when a 4-substituent is present, and viologen cation-radicals result if the 4-substituent constitutes a viable leaving group. Thus the 4,4'-dimer of 4-cyano-1-methyl-1-hydropyridinyl loses cyanide ion to give 1,1'-dimethyl-4,4'-bipyridinium ion and the latter is then reduced to the viologen. (Scheme 2; X = CN, R = Me, route *abef*)²³¹ The reducing agent is either the reductant of step *a* or the intermediate pyridinyl radical. Reduction of 3,5-di(ethoxycarbonyl)-1,2,6-trimethylpyridinium ion yields a mixture of isomeric dimers. An initial 2,4'-dimer, constituting the kinetic product, rearranges to give the thermodynamically more stable 4,4'-product via dissociation and recombination.²³²

²³⁰ D. Guerin-Ouler, C. Nicollin, C. Sieiro, and C. Lamy, *Mol. Phys.* **34**, 161 (1977).

²³¹ E. M. Kosower and J. L. Cotter, *J. Am. Chem. Soc.* **86**, 5524 (1964).

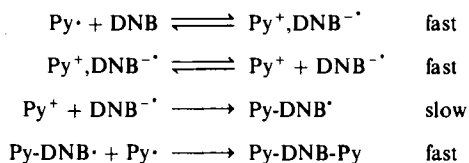
²³² F. T. McNamara, J. W. Niefert, J. F. Ambrose, and E. S. Huyser, *J. Org. Chem.* **42**, 988 (1977).

Kosower's radical (**66**) reacts with alkyl halides by a mechanism which transfers a halogen atom to the pyridinyl radical in the rate determining step (Py^\bullet is **66**):

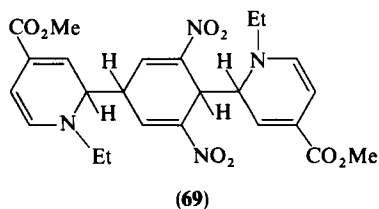
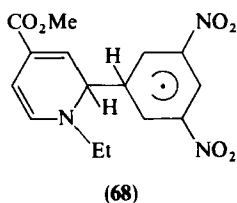


The initially formed chlorides PyX ionize to a pyridinium halide while PyR represents mixed 1,4- and 1,2-dihydropyridines.^{233,234} 4-Nitrobenzyl halides react by a different mechanism: the initial step here is electron transfer from **66** to the halide to give a nitro anion-radical which subsequently loses halide. Since this reaction involves ionic intermediates it is much more susceptible to solvent effects than the atom transfer reaction.^{235,236}

Mohammad has also found that benzoyl and 4-nitrobenzoyl chlorides parallel the benzyl halides, the one reacting with **66** by an atom transfer mechanism and the other by electron transfer, in the rate-determining step.²³⁷ By contrast, 1,3-dinitrobenzene, although a more powerful electron acceptor than 4-nitrobenzyl chloride, reacts slower than the latter with **66** (by a factor $> 10^5$), albeit by a mechanism whose initial step is electron transfer.²³⁸ The proposed mechanism is as follows:



Py-DNB^\bullet and Py-DNB-Py are suggested to be **68** and **69**, respectively.



²³³ E. M. Kosower and I. Schwager, *J. Am. Chem. Soc.* **86**, 5528 (1964).

²³⁴ M. Mohammad and E. M. Kosower, *J. Am. Chem. Soc.* **93**, 2709 (1971).

²³⁵ E. M. Kosower and M. Mohammad, *J. Am. Chem. Soc.* **90**, 3271 (1968).

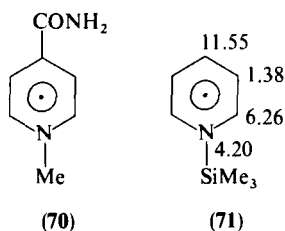
²³⁶ M. Mohammad and E. M. Kosower, *J. Am. Chem. Soc.* **93**, 2713 (1971).

²³⁷ M. Mohammad, *Aust. J. Chem.* **26**, 229 (1973).

²³⁸ M. Mohammad, *J. Chem. Soc., Perkin Trans. 2* p. 526 (1975).

Many 1-alkyl-1-hydropyridinyl radicals are not persistent in aqueous medium. The bimolecular decay reaction has been investigated for **66** and **70** and a mechanism consistent with products and kinetics advanced.²³⁹ The reactions of **70**, its 3-carboxamide isomer, and the pyridinyl radical derived from nicotinamide adenine dinucleotide (NAD) with cytochrome c have been investigated by pulse radiolysis and rates established.²⁴⁰

Reactions of simple pyridines with bis(trimethylsilyl)mercury results in the formation of 1,1'-bis(trimethylsilyl)-1,1',4,4'-tetrahydro-4,4'-bipyridines. These reversibly dissociate on heating in oxygen-free solution to yield 1-trimethylsilyl-1-hydropyridinyl radicals which have been characterized by ESR, e.g., **71** for which splittings are given in gauss.²⁴¹ If the pyridines bear



mesomerically electron-withdrawing substituents in the 4-position, reaction with the mercury reagent does not give dimeric products. The intermediate 1-trimethylsilyl-1-hydropyridinyl radicals are themselves further silylated in the 4-substituent and give diamagnetic products.²⁴² Other organometallic pyridinyls have also been prepared.^{242a}

Chemical and physical evidence has been obtained for the mediation of 1-acyl-1-hydropyridinyl radicals in the complex suite of reactions which ensues on thermolysis of 1,1'-diacyl-1,1',4,4'-tetrahydro-4,4'-bipyridines.^{243,244}

An important physical property of **66** and its simple 1-alkyl homologs is the capacity to form dimeric complexes in solution as the temperature is lowered. No covalent bond is formed: the complexes are believed to be π -complexes, and their formation is accompanied spectroscopically by the appearance of characteristic intermolecular charge-transfer transitions.²⁴⁵

²³⁹ E. M. Kosower, A. Teuerstein, and A. J. Swallow, *J. Am. Chem. Soc.* **95**, 6127 (1973).

²⁴⁰ E. J. Land and A. J. Swallow, *Ber. Bunsenges. Phys. Chem.* **79**, 436 (1975).

²⁴¹ B. Schroeder, W. P. Neumann, J. Hollaender, and H-P. Becker, *Angew. Chem. Int. Ed. Engl.* **11**, 850 (1972).

²⁴² S. V. Ponomarev, H-P. Becker, W. P. Neumann, and B. Schroeder, *Justus Liebigs Ann. Chem.* p. 1895 (1975).

^{242a} T. N. Mitchell, *J. Chem. Soc., Perkin Trans. 2* p. 1149 (1976).

²⁴³ P. Atlani, J. F. Biellmann, R. Brière, H. Lemaire, and A. Rassat, *Tetrahedron* **28**, 2827 (1972).

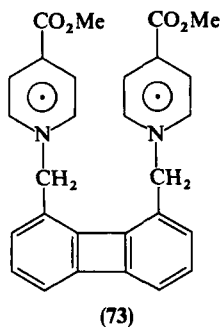
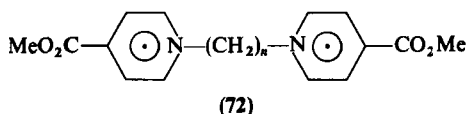
²⁴⁴ P. Atlani, J. F. Biellmann, R. Brière, and A. Rassat, *Tetrahedron* **28**, 5805 (1972).

²⁴⁵ M. Itoh and S. Nagakura, *J. Am. Chem. Soc.* **89**, 3959 (1967).

From a study of the consequences of π -complex formation for the UV spectra of pyridinyl radicals a geometry of the π -complex was proposed. As usual for such complexes, a parallel disposition of the aromatic planes was suggested, mutually oriented to minimize steric interactions between substituents.²⁴⁶

The electronic state of the dimeric π -complexes may be singlet or triplet. Two triplet states, differing in geometry, have been detected in methyltetrahydrofuran glasses.^{247,248}

Diradicals have been prepared with pyridinyl groups at either end of alkyl chains of varying length, e.g., **72**. Examination of their ESR and electronic absorption spectra showed that short chain lengths are associated with relatively low spin concentrations and strong visible absorptions but that their UV spectra are very comparable with monomeric **66**. These results were taken to indicate intramolecular association of the pyridinyl end-groups to give an essentially singlet species comparable with the bimolecular complexes of **66**.²⁴⁹ A triplet species was recognized, also, in glassy solution.²⁵⁰ Coordination of the diradicals by Mg^{2+} and other metal cations enhances the interaction of the radical end-groups^{251,252} Diradicals possessing pyridinyl functions attached to aromatic systems, e.g., **73**, have also been syn-



²⁴⁶ M. Itoh, *Chem. Phys. Lett.* **2**, 371 (1968).

²⁴⁷ Y. Ikegami, H. Watanabe and S. Seto, *J. Am. Chem. Soc.* **94**, 3274 (1972).

²⁴⁸ Y. Ikegami and S. Seto, *J. Am. Chem. Soc.* **96**, 7811 (1974).

²⁴⁹ M. Itoh and E. M. Kosower, *J. Am. Chem. Soc.* **90**, 1843 (1968).

²⁵⁰ E. M. Kosower and Y. Ikegami, *J. Am. Chem. Soc.* **89**, 461 (1967).

²⁵¹ E. M. Kosower and J. Hajdu, *J. Am. Chem. Soc.* **93**, 2354 (1971).

²⁵² E. M. Kosower, J. Hajdu, and J. B. Nagy, *J. Am. Chem. Soc.* **100**, 1186 (1978).

thesized, together with their Mg^{2+} complexes; and their photochemical decomposition was investigated.²⁵³

1-Alkyl-1-hydropyridinyl radicals form π -complexes with pyridinium ions. Itoh has studied the intramolecular association of the heterocyclic termini of cation-radicals, structurally analogous to **72**, but with one pyridinyl entity replaced by the corresponding pyridinium group, i.e., $\text{Py}^+-(\text{CH}_2)_n-\text{Py}^\cdot$.²⁵⁴ The proportion of the ring-closed form ranges from ca. 90% for $n = 3$ to ca. 0% for $n = 5$. Highly associated forms give low apparent spin concentrations and ESR spectra comparable with that of **66**. From this it is inferred that the detectable ESR signal derives from the low concentration of open-chain radical present and that the signal from the ring-closed form is broadened beyond detection by electron exchange between the pyridinyl and pyridinium units.

The isomeric bimolecular complexes of **66** with 1,1'-(1,3-propanediyl)-bis[4-(methoxycarbonyl)pyridinium] dication, i.e., $\text{Py}^+-(\text{CH}_2)_3-\text{Py}^+$, and of $\text{Py}^+-(\text{CH}_2)_3-\text{Py}^\cdot$ with methyl 1-ethylpyridinium-4-carboxylate have been studied. The former is converted thermally into the latter. Spectroscopic characteristics were also reported.²⁵⁵

Molecular complexes frequently exhibit two intermolecular charge-transfer transitions.²⁵⁶ The energy difference between the two such transitions in 1-alkylpyridinium iodides has been correlated with the HOMO-LUMO transition in the corresponding pyridinyl radicals, supporting the contention that the charge-transfer transitions have their origin in dual electron-acceptor levels.²⁵⁷

e. Other N-Substituted Hydroazinyl Radicals. 4-Cyano-1-methyl-1-hydroquinolinyl (**74**) has been prepared by several routes and its ESR spectrum analyzed (indicated hyperfine splittings are in gauss).²⁰⁹ Similarly, the ESR spectrum of 9-cyano-10-methyl-10-hydroacridinyl (**75**) has been assigned and the role of this radical in chemiluminescent reactions of lucigenin (10,10'-dimethyl-9,9'-biacridinium dinitrate) investigated.^{187,258,259} 9-*t*-Butyloxy-10-methyl-10-hydroacridinyl was also described.¹⁸⁷ Other workers have concluded that the diradical **76** is the first formed product in the chemiluminescent reaction of lucigenin with nucleophiles.²⁶⁰

²⁵³ E. M. Kosower and A. Teuerstein, *J. Am. Chem. Soc.* **100**, 1182 (1978).

²⁵⁴ M. Itoh, *J. Am. Chem. Soc.* **93**, 4750 (1971).

²⁵⁵ E. M. Kosower and A. Teuerstein, *J. Am. Chem. Soc.* **98**, 1586 (1976).

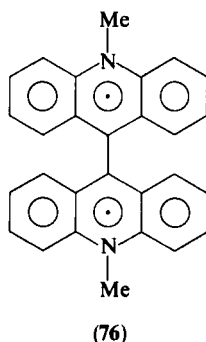
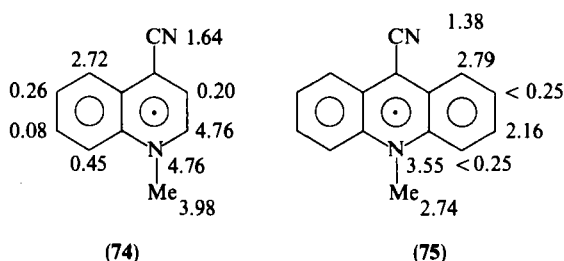
²⁵⁶ R. Foster, "Organic Charge Transfer Complexes," p. 67. Academic Press, New York, 1969.

²⁵⁷ E. M. Kosower, E. J. Land, and A. J. Swallow, *J. Am. Chem. Soc.* **94**, 986 (1972).

²⁵⁸ J. W. Happ, E. G. Janzen, and B. C. Rudy, *J. Org. Chem.* **35**, 3382 (1970).

²⁵⁹ E. G. Janzen, J. B. Pickett, J. W. Happ, and W. DeAngelis, *J. Org. Chem.* **35**, 88 (1970).

²⁶⁰ K. Maeda, T. Kashiwabara, and M. Tokuyama, *Bull. Chem. Soc. Jpn.* **50**, 473 (1977).



10-Methyl-10-hydroacridinyl radicals are involved in the electrochemical oxidation of 10-methyl-9,10-dihydroacridines with at least one of the 9-positions unsubstituted. If both 9-positions are substituted, 10-hydroacridinyl radicals are not involved since loss of a methylene proton from the initially formed 9,10-dihydroacridine cation-radical is impossible.²⁶¹

A reinterpretation has appeared of the behavior of 5-ethyl-5-hydrophenazinyl in solution on lowering the temperature.²⁶² Originally, it was concluded that the radical dimerized to a diamagnetic form.²⁶³⁻²⁶⁵ Now, however, it is believed that diamagnetic crystallites are formed. Characteristic spectroscopic absorptions which appear as paramagnetism is lost are also ascribed to the solid phase.^{262,266} Electronic fluorescence spectra of 5-ethyl-5-hydrophenazinyl have been reported as have pK values for its ground and first excited states.²⁶⁷ An interpretation of the ESR spectrum of this radical has also been published.²⁶⁸

²⁶¹ E. Sturm, H. Kiese, and E. Daltrozzo, *Chem. Ber.* **111**, 227 (1978).

²⁶² O. Serafimov and H. Zimmerman, *Ber. Bunsenges. Phys. Chem.* **76**, 904 (1972).

²⁶³ K. H. Hausser and L. Birkofer, *Naturwissenschaften* **42**, 97 (1955).

²⁶⁴ K. H. Hausser, *Z. Naturforsch., Teil A* **11**, 20 (1956).

²⁶⁵ K. H. Hausser and J. N. Murrell, *J. Chem. Phys.* **27**, 500 (1957).

²⁶⁶ T. Sakata and S. Nagakura, *Bull. Chem. Soc. Jpn.* **42**, 1497 (1969).

²⁶⁷ W. Rubaszewska and Z. R. Grabowski, *J. Chem. Soc., Perkin Trans 2* p. 417 (1975).

²⁶⁸ J. Dobkowski and W. Rubaszewska, *Rocz. Chem.* **50**, 1435 (1976); *Chem. Abstr.* **86**, 15933 (1977).

3. Cation-Radicals

This Section deals with radicals which, although cationic, are $(4n + 3)$ electron species and are thus isoelectronic with azine anion-radicals. They may, in principle, occur for any azine, monocyclic or polycyclic, which possesses at least two nitrogen atoms, for it is substitution at these hetero-atoms which confers the positive charge, e.g., **17**, the diconjugate acid of **22**, and **37** (R = alkyl) its dialkyl derivative. Reviews which cover material pertinent to this Section are those of Forrester, Hay, and Thomson,⁴ of Nelsen,⁵ of Siskin⁸ and, most recently, of Bard, Ledwith, and Shine.¹¹

a. Preparation. Two general routes are available: the more common is reduction of the appropriate diquaternary ion; less common is the oxidation of the appropriate nonaromatic dihydro compound. Comproportionation, where the diquaternary compound serves as oxidant for the dihydro compound is frequently valuable. Acidic conditions are usually necessary for N-protonated radicals but less essential for N-alkylated radicals. Many of these cation-radicals are isolable as salts, although others are autoxidized or prone to deterioration in the presence of nucleophiles. These properties are indicated for individual families.

b. Viologen (Bipyridiniumyl) Radicals and Similar Species. Reduction of 4,4'-bipyridyl in acidic media, either by a dissolving metal or electrochemically, gives the simplest viologen radical **77**, the disconjugate acid of **50**.^{269,270} It is persistent in the absence of oxygen. The ESR spectrum of **77** was described by several groups in the early 1960s.²⁷⁰⁻²⁷⁴ The hyperfine splittings indicated (in gauss) in **77** are those of Barton and Fraenkel.²⁷⁴

The ESR spectrum of the 1,1'-dimethyl viologen radical (**78**) was observed at the same time.²⁷² It has since been recorded many times, together with those of other dialkyl viologen radicals.^{230,275-277} Polarographic studies of the formation of both **77** and **78**, their isomers, and derivatives have been

²⁶⁹ J. E. Volke and V. Volkova, *Collect. Czech. Chem. Commun.* **37**, 3686 (1972).

²⁷⁰ J. R. Bolton, A. Carrington and J. dos Santos-Veiga, *Mol. Phys.* **5**, 465 (1962).

²⁷¹ C. S. Johnson, R. E. Visco, H. S. Gutowsky, and A. M. Hartley, *J. Chem. Phys.* **37**, 1580 (1962).

²⁷² C. S. Johnson and H. S. Gutowsky, *J. Chem. Phys.* **39**, 58 (1963).

²⁷³ F. Bruin, F. W. Heineken, M. Bruin, and A. Zahlan, *J. Chem. Phys.* **36**, 2783 (1962).

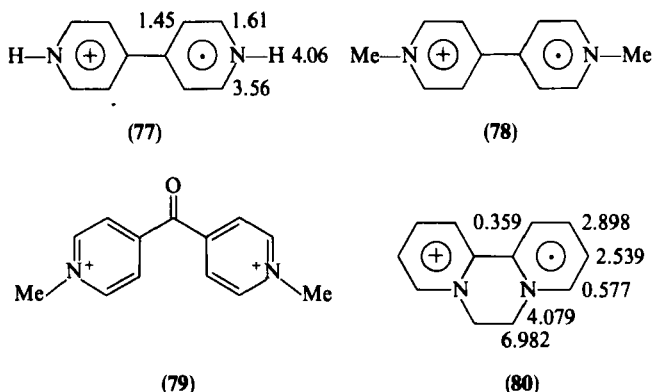
²⁷⁴ B. L. Barton and G. K. Fraenkel, *J. Chem. Phys.* **41**, 1455 (1964).

²⁷⁵ B. I. Shapiro, V. V. Minin, and Ya. K. Syrkin, *Zh. Strukt. Khim.* **14**, 642 (1973); *Chem. Abstr.* **79**, 125401 (1973).

²⁷⁶ A. G. Evans, J. C. Evans, and M. W. Baker, *J. Chem. Soc., Perkin Trans. 2* p. 1787 (1977).

²⁷⁷ A. G. Evans, J. C. Evans, and M. W. Baker, *J. Am. Chem. Soc.* **99**, 5882 (1977).

reported.^{278,279} Mention has already been made of the formation of **78**, on reduction of both 1-methylpyridinium ion and its 4-cyano derivative.^{230,231,280} It is also apparently formed upon treatment of the ketone **79** with strong alkali.²⁸¹ The chemistry of **78** has been reviewed in detail: the reader is referred to ref. 11 and to other references cited therein. The great interest in **78** is on account of its role in the herbicidal properties of "Paraquat" (1,1'-dimethyl-4,4'-bipyridinium dichloride) which gives **78** upon one-electron reduction.¹¹



A similarly effective herbicide is "Diquat" (6,7-dihydrodipyrido[1,2-*a*:2',1'-*c*]pyrazine-di-ium dibromide) which undergoes one-electron reduction to give the bridged 2,2'-bipyridiumyl cation-radical **80**, equally implicated in herbicidal activity. The ESR spectrum of **80** has been analyzed by Sullivan and Williams.²⁸² No hyperfine splittings were resolved for two of the four methylene protons. The authors favored an explanation invoking a line broadening due to libration in the bridging group rather than a fixed conformation. Sullivan and co-workers have also studied the analog of **80** with only one bridging methylene group.²⁸³ In this case the methylene protons give equivalent and exceptionally large hyperfine splittings, a phenomenon explained in terms of the symmetry of the singly occupied orbital: the coefficients at both the N atoms attached to the methylene group are large and of the same sign.²⁸³

²⁷⁸ S. Hünig, J. Gross, and W. Schenk, *Justus Liebigs Ann. Chem.* p. 324 (1973).

²⁷⁹ S. Hünig, B. J. Garner, G. Ruider, and W. Schenk, *Justus Liebigs Ann. Chem.* p. 1036 (1973).

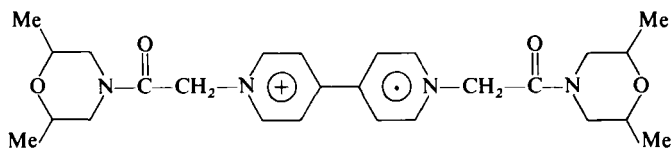
²⁸⁰ M. Naarova and J. Volke, *Collect. Czech. Chem. Commun.* **38**, 2670 (1973).

²⁸¹ F. E. Geiger, C. L. Trichilo, F. L. Minn, and N. Filipescu, *J. Org. Chem.* **36**, 357 (1971).

²⁸² P. D. Sullivan and M. L. Williams, *J. Am. Chem. Soc.* **98**, 1711 (1976).

²⁸³ P. D. Sullivan, J. Y. Fong, M. L. Williams, and V. D. Parker, *J. Phys. Chem.* **82**, 1181 (1978).

The chemistry of bipyridiniumyl radicals reported since the previous review¹¹ includes a study by Evans and co-workers of the dimerization equilibria of **78**, **80** and other alkyl homologs of the former.^{276,277} On cooling methanol solutions of the cation-radicals, the paramagnetism decreases. It was shown that the behavior is consistent with dimerization and not disproportionation. From the measured entropy change, it was concluded that marked desolvation of the cation-radicals occurs on dimerization. This was taken to imply a configuration in the dimer requiring parallelism of the aromatic planes. A comparable study was carried out for the radical **81** obtained by one electron reduction of the herbicide "Morphamquat."²⁸⁴



(81)

Evans and co-workers have studied, additionally, the kinetics of the reactions of **78**, **80**, and **81** with molecular oxygen and other oxidants (Cr^{3+} , Cu^{2+}) and the consequences for them of the dimerization equilibria.²⁸⁵⁻²⁸⁷ Thorneley has also studied the reaction of **78** with oxygen, confirming that hydrogen peroxide is formed.²⁸⁸ The reaction with oxygen to produce hydrogen peroxide, which is believed to be a key step in the herbicidal role of the bipyridiniumyl radicals, has also been made the basis of analytical procedures to determine oxygen.^{289,290} Radical **78** has been used in an analytical role in determining the lifetime of a Norrish type II biradical.²⁹¹ Various workers have investigated the reduction of cytochrome c by **78** and a range of related radicals.^{240,292,293}

In the search for new herbicides and for information on factors which influence the herbicidal properties of bipyridinium ions, many substances have been synthesized, especially by Summers and co-workers. Structural

²⁸⁴ A. G. Evans, J. C. Evans, and M. W. Baker, *J. Chem. Soc., Perkin Trans. 2* p. 1310 (1975).

²⁸⁵ A. G. Evans, R. E. Alford, and N. H. Rees, *J. Chem. Soc., Perkin Trans. 2* p. 1831 (1975).

²⁸⁶ A. G. Evans, N. K. Dodson, and N. H. Rees, *J. Chem. Soc., Perkin Trans. 2* p. 859 (1976).

²⁸⁷ A. G. Evans, R. E. Alford, and N. H. Rees, *J. Chem. Soc., Perkin Trans. 2* p. 445 (1977).

²⁸⁸ R. N. F. Thorneley, *Biochim. Biophys. Acta* **333**, 487 (1974).

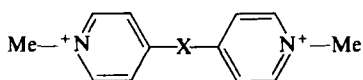
²⁸⁹ P. B. Sweetser, *Anal. Chem.* **39**, 979 (1967).

²⁹⁰ R. E. van der Leest, *J. Electroanal. Chem. Interfacial Electrochem.* **43**, 251 (1973).

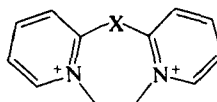
²⁹¹ R. D. Small and J. C. Scaiano, *J. Phys. Chem.* **81**, 828 (1977).

²⁹² M. G. Simic, I. A. Taub, J. Tocci, and P. A. Hurwitz, *Biochem. Biophys. Res. Commun.* **62**, 161 (1975).

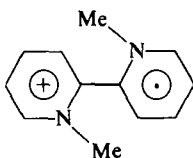
²⁹³ L. Mackey, E. Steckhan, and T. Kuwana, *Ber. Bunsenges. Phys. Chem.* **79**, 587 (1975).



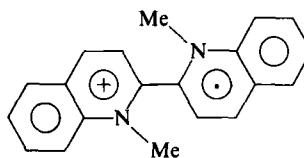
(82)



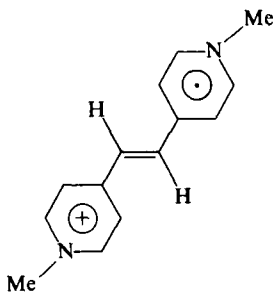
(83)



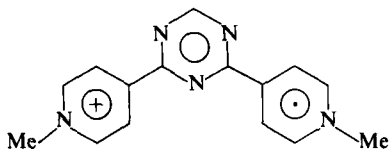
(84)



(85)



(86)



(87)

variations have involved relatively simple substitutions of the earlier mentioned herbicides,²⁹⁴⁻³⁰⁰ or more drastic modification giving, for example, **82** ($X = S, NH$) and **83** ($X = S, C=O, C=CH_2$).³⁰¹⁻³⁰⁶ Although of variable efficacy as herbicides, many of the materials have been shown to undergo one-electron reduction to give cation-radicals.

The persistent cation-radicals **84-87** have been prepared.³⁰⁷⁻³¹⁰ Summers and co-workers have alluded to ESR spectra of some of their radicals but

²⁹⁴ R. Fielden and L. A. Summers, *J. Heterocycl. Chem.* **11**, 299 (1974).

²⁹⁵ P. M. Pojer and L. A. Summers, *J. Heterocycl. Chem.* **11**, 303 (1974).

²⁹⁶ K. J. Schmalzl and L. A. Summers, *Chem. Ind. (London)* p. 652 (1975).

²⁹⁷ N. H. Pirzada, P. M. Pojer, and L. A. Summers, *Z. Naturforsch., Teil B* **31**, 115 (1976).

²⁹⁸ A. L. Black and L. A. Summers, *J. Heterocycl. Chem.* **8**, 29 (1971).

²⁹⁹ J. E. Downes, *J. Chem. Soc. C* p. 1491 (1967).

³⁰⁰ J. E. Downes, *J. Chem. Soc. C* p. 2192 (1967).

³⁰¹ J. E. Dickeson and L. A. Summers, *J. Heterocycl. Chem.* **7**, 719 (1970).

³⁰² L. A. Summers, *Tetrahedron* **24**, 2697 (1968).

³⁰³ A. L. Black and L. A. Summers, *J. Chem. Soc. C* p. 2394 (1970).

³⁰⁴ I. F. Eckhard and L. A. Summers, *Aust. J. Chem.* **27**, 2511 (1974).

³⁰⁵ N. H. Pirzada and L. A. Summers, *Z. Naturforsch., Teil B* **31**, 122 (1976).

³⁰⁶ L. A. Summers, *Naturwissenschaften* **54**, 491 (1967).

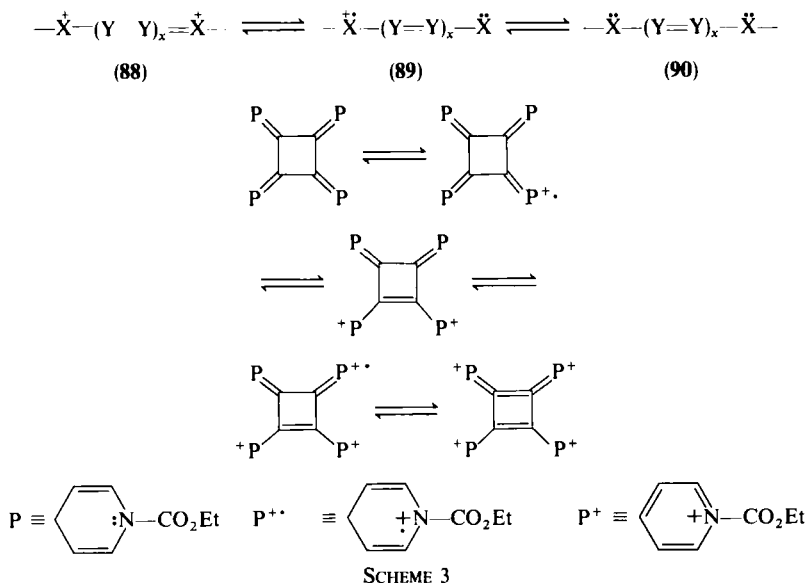
³⁰⁷ L. A. Summers, *Z. Naturforsch., Teil B* **29**, 89 (1974).

³⁰⁸ J. E. Dickeson and L. A. Summers, *J. Heterocycl. Chem.* **7**, 401 (1970).

³⁰⁹ H. Fischer and L. A. Summers, *Tetrahedron* **32**, 615 (1976).

³¹⁰ J. E. Dickeson and L. A. Summers, *J. Chem. Soc. C* p. 1643 (1969).

have not published details. Others have, however, analyzed the ESR spectrum of **86** which occurs predominantly in the trans form whether derived from the cis or trans diquaternary precursor.³¹¹ Hünig and co-workers have characterized **84**, **86** and phenylogous and diazavinyllogous bipyridiniumyl radicals polarographically.^{278,312,313} This work has been part of an intensive study by the German school of the violenes, compounds containing structural units of the type **88** where X is usually a heteroatom, e.g., N or S, and Y—Y is a vinylic or diazavinyl group. Violenes undergo stepwise one-electron reductions giving the neutral **90** via the cation-radical **89**. Violenes are relevant in the present context when X is part of a $(4n + 3)$ -electron heteroaromatic moiety. [The total number of electrons in a violene cation-radical is also $(4n + 3)$ when x in **89** is even, but it is $(2n + 3)$ for odd x .] The approach of the present review fragments the body of work on violenes, separating those with heteroaromatic components from those without and further dividing the former by ring size and heteroatomic make-up. The reader is referred to the articles by Hünig for an integrated overview.³¹⁴ Mention has already been made of the relationship of the disproportionation equilibria of **20** and **21** to the extent of conjugation in these systems.³³ Other theoretical work has been reported by the same group.³¹⁵ Recently, Horner and Hünig have described the remarkable series of redox equilibria shown in Scheme 3.



³¹¹ J. W. Happ, J. A. Ferguson, and D. G. Whitten, *J. Org. Chem.* **37**, 1485 (1972).

³¹² S. Hünig and J. Gross, *Tetrahedron Lett.* p. 2599 (1968).

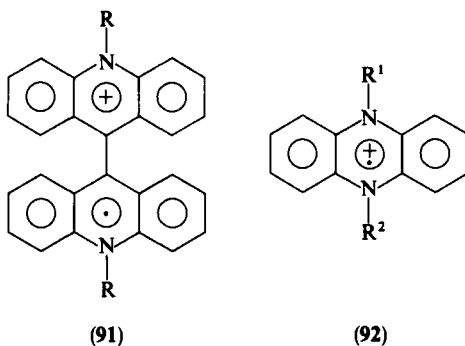
³¹³ S. Hünig and G. Ruider, *Justus Liebigs Ann. Chem.* p. 1415 (1974).

³¹⁴ S. Hünig, *Pure Appl. Chem.* **15**, 109 (1967).

³¹⁵ S. Hünig, D. Scheutzw, P. Carsky, and R. Zahradnik, *J. Phys. Chem.* **75**, 335 (1971).

Bernasconi and co-workers have studied the kinetics of disproportionation-comproportionation in azaviolene systems by temperature jump, stopped-flow, and pH jump techniques, examining the electron transfer process in the light of Marcus theory.³¹⁶⁻³¹⁸

On photoreduction of 9,9'-biacridine in ethanol, Niizuma *et al.* obtained the radical-cation **91** (R = H) and analyzed its ESR spectrum.³¹⁹ The corresponding radical **91** (R = Me) has been prepared by electron transfer from carbanions to lucigenin.²⁶⁰ Its ESR spectrum has been analyzed by Janzen and co-workers.²⁵⁹



c. Dihydrodiaziniumyl Radicals and Related Species. 1,4-Dihydrodiaziniumyl radicals are persistent species, often in the presence of air; several ESR spectra were solved some years ago. Thus **17** was described by Bolton *et al.*,²⁷⁰ who also assigned the spectrum of 9,10-dihydrophenaziniumyl **92** (R¹ = R² = H). The radicals were generated by reduction with Zn in acid. Barton and Fraenkel too, described these radicals, obtained by electrochemical reduction of the parent diazines in acidified DMF.²⁷⁴ In addition, they assigned the ESR spectra of several C-methylated derivatives of **17** and of 1,4-dihydroquinoxaliniunyl and its 2,3-dimethyl derivative.

Some of these cation-radicals have been generated in aqueous or alcoholic solutions by photolytic methods.^{196,197,209,216} ESR assignments for 1,3-dihydropyrimidinunyl and 1,2-dihydropyridazinunyl radicals as well as the isomeric **17** were obtained for aqueous solutions.¹⁹⁶ The same three dihydrodiaziniumyl radicals have also been generated by pulse radiolysis, as was 1,4-dihydroquinoxaliniunyl, and spectroscopic, kinetic, and pK data

³¹⁶ C. F. Bernasconi, R. G. Bergstrom, and S. Hünig, *Chem. Commun.* p. 1485 (1971).

³¹⁷ C. F. Bernasconi, R. G. Bergstrom, and W. J. Boyle, *J. Am. Chem. Soc.* **96**, 4643 (1974).

³¹⁸ C. F. Bernasconi and H.-C. Wang, *J. Am. Chem. Soc.* **99**, 2214 (1977).

³¹⁹ S. Niizuma, K. Nakamaru, and M. Kuizumi, *Chem. Lett.* p. 59 (1972).

obtained.²¹⁹ The protio- and deuterio-diconjugate acids of **55** ($R = \text{Me}$) were obtained by Gerson and Skorianetz and their ESR spectra assigned.¹⁴⁴

The stable chloride salt of **92** ($R^1 = R^2 = \text{H}$) was unexpectedly obtained on treatment of phenazine with the ion UOCl_2^- in moist nitromethane. Similarly prepared were cation-radical salts of benzophenazines and 2,3-bis(2-pyridyl)quinoxaline.^{320,321} A kinetic study of the relative reactivity of **92** ($R^1 = R^2 = \text{H}$) and the fully reduced 9,10-dihydrophenazine in electron transfer to an azo compound showed the cation-radical is the less reactive.³²² Soviet workers have examined the consequence of ring substitution for the spin distribution in a series of 9,10-dihydrophenaziniumyl radicals.³²³

Only pyrazine among the monocyclic diazines forms well characterized N,N' -dialkylated cation-radicals: Ahn and Johnson have presented detailed studies of line-shape variation in the ESR spectra of 1,4-dimethyl and 1,4-diethyl-1,4-dihydropyraziniumyl radicals.^{324,325} Although diquaternary salts of all three simple diazines have been prepared, it was found that only the dialkylated pyrazine underwent spontaneous reduction to the cation-radical in alcoholic solution.³²⁶

A synthetic procedure for obtaining **92** ($R^1 = \text{Me}$, $R^2 = \text{H}$) has been given,³²⁷ and the role of the same radical as an "electron bridge" in biometric reactions described.³²⁸ Its fluorescence spectrum and protolytic characteristics in ground and excited states have also been discussed.²⁶⁷

The ESR spectrum of **92** ($R^1 = R^2 = \text{Me}$) was assigned by Nelson *et al.*³²⁹ following generation of the radical by anodic oxidation of the corresponding 5,10-dihydrophenazine.

Cauquis and co-workers have generated **92** ($R^1 = R^2 = \text{Ph}$) and several variously substituted congeners by the anodic oxidation of phenylene diamines.³³⁰⁻³³²

³²⁰ J. Selbin, D. G. Durrett, H. J. Sherrill, G. R. Newkome, and J. H. Wharton, *Chem. Commun.* p. 380 (1972).

³²¹ J. Selbin, D. G. Durrett, H. J. Sherrill, G. R. Newkome, and M. Collins, *J. Inorg. Nucl. Chem.* **35**, 3467 (1973).

³²² R. L. Reeves, *Can. J. Chem.* **48**, 2718 (1970).

³²³ L. L. Gordienko and A. G. Chukhlantseva, *Teor. Eksp. Khim.* **5**, 844 (1969); *Chem. Abstr.* **72**, 110440 (1970).

³²⁴ M.-K. Ahn and C. S. Johnson, *J. Chem. Phys.* **50**, 632 (1969).

³²⁵ M.-K. Ahn and C. S. Johnson, *Proc. Colloq. AMPERE* **14**, 253 (1966); *Chem. Abstr.* **69**, 101631 (1968).

³²⁶ T. J. Curphey and K. S. Prasard, *J. Org. Chem.* **37**, 2259 (1972).

³²⁷ Y. Takagi, K. Akasaka, T. Imoto, H. Kawai, and K. Ishizu, *Chem. Lett.* p. 847 (1972).

³²⁸ N. Kito, Y. Ohnishi, M. Kagami, and A. Ohno, *Chem. Lett.* p. 353 (1974).

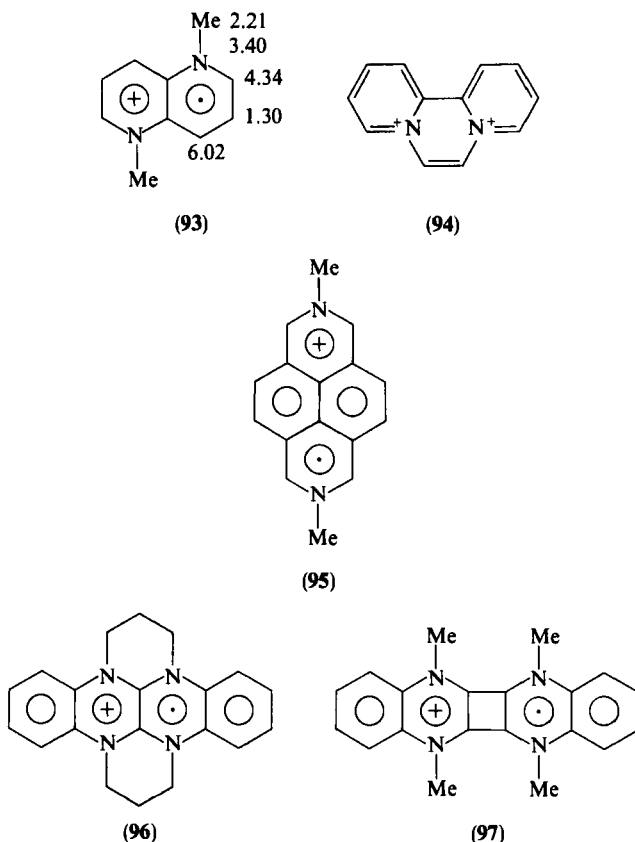
³²⁹ R. F. Nelson, D. W. Leedy, E. T. Seo, and R. N. Adams, *Z. Anal. Chem.* **224**, 184 (1967).

³³⁰ G. Cauquis, H. Delhomme, and D. Serve, *Tetrahedron Lett.* p. 4113 (1971).

³³¹ G. Cauquis, H. Delhomme, and D. Serve, *Tetrahedron Lett.* p. 4649 (1971).

³³² G. Cauquis and D. Serve, *Tetrahedron Lett.* p. 2695 (1973).

d. *Polycyclic Dihydroazine Cation-Radicals*. Summers and co-workers³³³ found that the *N,N'*-dimethyl diquaternary salt of 1,5- but not 1,8-naphthyridine is reduced to a persistent cation-radical **93**. The ESR spectrum of **93** and that of its dihydro analog have been unequivocally analyzed by Sullivan and Paudler.³³⁴ (Splittings in structure **93** in gauss.) The hyperfine splitting from the methyl protons in **93** is unexpectedly small. Usually, in *N*-methylated cation-radicals the ratio $a(\text{N})/a(\text{Me})_{\text{N}}$ is about 1.05, implying reasonable constancy of the Q values [cf. Eqs. (2), (5), and (12)]; here it is 1.54. That the behavior of the nitrogen splitting is normal is indicated by a usual $a(\text{N})/a(\text{H})_{\text{N}}$ ratio in the dihydro derivative and by an average increase in $a(\text{N})$ upon methylation. The authors discount a steric cause for the anomaly for want of a temperature dependence and suggest that the



³³³ J. E. Dickeson, I. F. Eckhard, R. Fielden, and L. A. Summers, *J. Chem. Soc., Perkin Trans. 1* p. 2885 (1973).

³³⁴ P. D. Sullivan and W. W. Paudler, *Can. J. Chem.* **51**, 4095 (1973).

reason lies in the charge distribution of the radical. The nature of the reaction which results in the lack of persistence in unmethylated 1,5-naphthyridine cation-radicals has been investigated; a dimerization following a rate-determining unimolecular rearrangement is suggested.³³⁵

The existence of cation-radicals derived from protonated or alkylated phenanthrolines has been indicated polarographically and by other studies, but no ESR spectra of such species have been assigned.^{312,336-338}

The aromatic dication, dipyrido[1,2-*a*;2',1'-*c*]pyrazinium (**94**), has been shown to undergo reduction to a cation-radical which is reoxidized back to **94** by oxygen in high yield. Consistent with this behavior and its structural relationship with Diquat, **94** is a potent herbicide.

Comparison of the ESR spectra of **95** and its dihydro analog with that of **59** shows a remarkable relative increase in nitrogen splitting in the cation-radicals.¹⁹² The nitrogen hyperfine splittings are 1.57, 4.07, and 4.39 G, respectively, for **59**, its diconjugate acid, and **95**. By contrast, the difference in nitrogen splittings between **50** and **77** is very small. The change was rationalized following HMO calculations which showed that, unlike the 4,4'-bipyridyl case, the energy sequence of the lowest antibonding orbitals in 2,7-diazapyrene is critically dependent on the Coulomb integral of the heteroatoms. Protonation or methylation enhances the electronegativity of the heteroatom, thus it appears that in the N-substituted 2,7-diazapyrenes the LUMO is of different symmetry to the LUMO in the parent heterocycle. In the derived radicals, therefore, different orbitals are singly occupied in the anion on the one hand and in the cations on the other. The change in proton splittings between the two charge types is in agreement.

Radical **95** has also been characterized polarographically, as have **96**, **97**, and various diazoniapentaphenes.^{336,339,340}

B. AZINE CATION-RADICALS

This Section is concerned with $(4n + 1)$ electron species, e.g., **2**, which arise by removal of an electron from the HOMO of an azine.

It is only within the past 5 years that convincing evidence for the existence of the pyridine cation-radical (**2**) has been presented. Previously, the only allusion to the possible existence of **2** was that by Grimison and Simpson,

³³⁵ L. Roullier and E. Laviron, *Electrochim. Acta* **21**, 421 (1976).

³³⁶ S. Hünig, J. Gross, E. F. Lier, and H. Quast, *Justus Liebigs Ann. Chem.* p. 339 (1973).

³³⁷ L. A. Summers, *Tetrahedron* **24**, 5433 (1968).

³³⁸ A. L. Black and L. A. Summers, *Tetrahedron* **24**, 6453 (1968).

³³⁹ S. Hünig, D. Scheutzow, and H. Schlaff, *Justus Liebigs Ann. Chem.* **765**, 126 (1972).

³⁴⁰ S. Hünig and H. Pütter, *Angew. Chem., Int. Ed. Engl.* **12**, 149 (1973).

who generated a cationic species from pyridine by radiolysis at low temperatures in a Freon matrix.³⁴¹ The species had an absorption band at 380 nm; however, the authors were uncertain whether it was the true cation-radical or some derived entity. In 1974, Ledwith and Russell reported the oxidation of pyridine by peroxydisulfate.³⁴² These workers found that the major products at neutral and acid pH were isomeric pyridylpyridinium ions, e.g., **98**, and suggested that they arise by oxidation of the products of nucleophilic attack of pyridine upon **2**, itself formed by electron transfer from pyridine to $\text{SO}_4^{\cdot -}$. Minor yields of isomeric bipyridyls were also obtained, the amounts of which were increased in basic conditions; a deprotonation of **2** to give **14**, with subsequent reactions of the latter, was suggested in explanation. Polycarboxylic acids of benzene and pyridine have also been oxidized by $\text{SO}_4^{\cdot -}$ to yield aryl σ -radicals possessing fewer carboxyl groups.³⁴³ A high degree of selectivity in decarboxylation was observed, favoring 2-pyridyl radicals from appropriate pyridine substrates. This was interpreted to mean "oxidation of the molecule as a whole," followed by loss of a preferred carboxyl group, as opposed to direct attack by $\text{SO}_4^{\cdot -}$ on a particular carboxyl group. Given this, preferred loss of a 2-proton from **2** to yield **14** would seem plausible. The implied oxidation of the arenes to the corresponding cationic π -radicals has been supported by mechanistic studies in the benzene series.³⁴⁴

The proportions of pyridylpyridinium salt isomers obtained as major products by Ledwith and Russell were 90:9:1 for the 2-, 3-, and 4-isomers, respectively.³⁴² The symmetry of the singly occupied π -orbital in **2** (i.e., ψ_3 in Fig. 2) is such that if the reactivity were governed by the Hückel π -orbital only, equal proportions of the 2-, and 3-pyridylpyridinium salts would be expected. Clearly, the results do demonstrate the dominant reactivity of the 2- and 3-positions, in sharp contrast with the preferred site of reaction in the anion and neutral radicals derived from this heterocycle. The unequal reactivities at the 2- and 3-positions may reflect the inductive effect of the heteroatom in the σ -electron framework of which the HOMO treatment takes no cognizance.

On account of its reactivity, no direct ESR evidence for the existence of **2** is available. Ledwith and Russell presented indirect evidence, claiming to have trapped **2** according to Eq. (13).³⁴² However, if the preferred site of reaction of **2** with nucleophilic species is the 2-position, it is surprising that reaction with the spin trap **99** should occur at the 1-position. Maybe the observation of **100** is an artefact of the type noted by Forrester and Hepburn,³⁴⁵ possibly arising by Eq. (14). In view of this, the alleged trapping

³⁴¹ A. Grimison and G. A. Simpson, *J. Phys. Chem.* **72**, 1776 (1968).

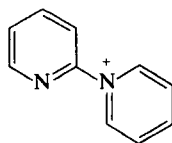
³⁴² A. Ledwith and P. J. Russell, *J. Chem. Soc., Perkin Trans.* **2** p. 582 (1974).

³⁴³ H. Zemel and R. W. Fessenden, *J. Phys. Chem.* **79**, 1419 (1975).

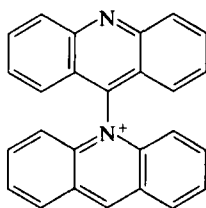
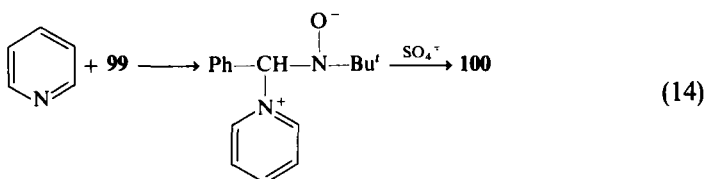
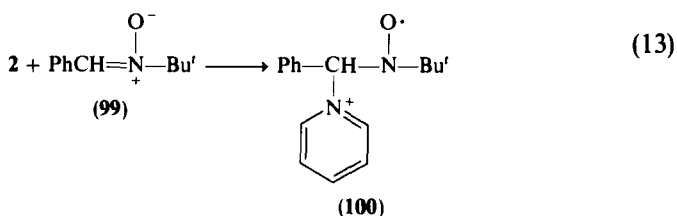
³⁴⁴ P. Neta, V. Madhavan, H. Zemel, and R. W. Fessenden, *J. Am. Chem. Soc.* **99**, 163 (1977).

³⁴⁵ A. R. Forrester and S. P. Hepburn, *J. Chem. Soc. C* p. 701 (1971).

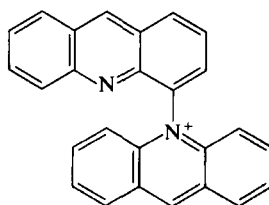
of 4-acetylpyridine cation-radical by **99** during the reaction of 4-acetylpyridine with the adamantyl radical should be viewed, perhaps, with circumspection.³⁴⁶



(98)



(101)



(102)

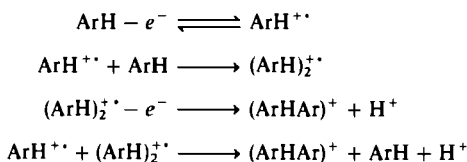
Marcoux and Adams have carried out a study of the anodic oxidation of a range of azines in acetonitrile at a platinum electrode.³⁴⁷ With the exception of pyridine which could not be oxidized under these conditions, all the other azines were oxidized in a complicated process in which one electron per molecule was transferred to the electrode. The reaction was investigated in some detail for acridine, and the main product was found to be an acridyl-acridinium perchlorate (perchlorate being supplied by the supporting electrolyte). This result, which is directly comparable with that for pyridine oxidation by peroxydisulfate is persuasive evidence for the mediation of the

³⁴⁶ M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Chem. Commun.* p. 329 (1976).

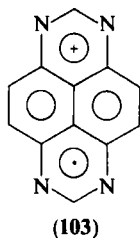
³⁴⁷ L. Marcoux and R. N. Adams, *J. Electroanal. Chem. Interfacial Electrochem.* **49**, 111 (1974).

acridine cation-radical. Structure **101** was suggested for the product, but in the Hückel approximation the HOMO of acridine, which is the singly occupied orbital of its cation, has the greatest coefficient at carbon at position 4.³⁴⁸ Thus, the product may alternatively be **102**, on the assumption that it is determined by interaction of the half-filled orbital of the cation-radical with the lone pair of an acridine molecule, as was suggested for the case of pyridine.

The results of potential-dependent chronocoulometric measurements suggested the mechanism of Scheme 4 for the reaction sequence, where ArH is acridine and (ArHAr)⁺ is **101** or **102**.³⁴⁷ The rate constant for the addition of acridine to its cation-radical was determined as 1.3×10^5 liter mol⁻¹ sec⁻¹.



SCHEME 4



The only azine cation-radical to have been characterized in solution by ESR seems to be that of 1,3,6,8-tetraazapyrene, (pyrimido[4,5,6-*gh*]perimidine) (**103**). The ESR spectrum of this radical is closely similar to that of **58**, the corresponding $(4n + 3)$ -electron radical, as would be expected.¹⁹¹ Sevilla has described cation-radicals from thymidine and various derivatives generated by photoionization in a glassy matrix.³⁴⁹

C. RADICALS FROM OXYGENATED AZINES

1. Azine N-Oxide Radicals

a. Anions. Azine *N*-oxides have given both anion- and cation-radicals. The anion-radical (**104**) of pyridine *N*-oxide and its simple derivatives were

³⁴⁸ See, for example, Streitwieser,²⁸ p. 331.

³⁴⁹ M. D. Sevilla, *J. Phys. Chem.* **80**, 1898 (1976).

obtained simultaneously with those of the unoxidized pyridines.^{29,79-82,350,351} The radicals were prepared by electroreductive methods in largely nonaqueous media. Reduction by potassium in DME led to loss of oxygen in certain circumstances,³⁵² and polarographic reduction in aqueous solution was shown to proceed by a two-electron step involving the conjugate acid of the substrate.³⁵³

The hyperfine splittings for **104** (shown in gauss) may be compared with those for **1** (Table I); it may be seen that *N*-oxidation does not greatly perturb the spin distribution. As with 4-nitropyridine anion-radical (**41**), the calculated spin distribution in the corresponding *N*-oxide radical-anion (**7**) depends on the MO method used.^{79,81,350} Nevertheless, however the assignment is made, the results of Itoh *et al.*⁸¹ indicate that the oxidized pyridine is more effective than the unoxidized heterocycle in delocalizing spin from the principal site in the nitro group. This is reasonable: mesomeric donation of electron density by O to the heterocycle reduces the capacity of the heterocycle to delocalize anionic charge which, it was argued in Section III,A,1,b, is the principal means whereby the spin distribution is regulated. Nevertheless, the fact of being oxidized increased the electron affinity of the pyridine *N*-oxides relative to the unoxidized pyridines.³⁵⁴

Janzen and Happ generated a series of 2- and 4-acylated pyridine *N*-oxide radical-anions by the autoxidation of corresponding alkyl or hydroxyalkyl precursors in mixtures of DMSO or DMF with *t*-butanol containing potassium *t*-butoxide.³⁵⁵ The computational approach of these workers to the spin distribution problem was rather different from that of the Japanese group,³⁵¹ but their results and conclusions were essentially concordant.

The theoretical account of the electronic absorption spectra of pyridine *N*-oxide radicals has also attracted interest.^{79,356}

Besides results for pyridine *N*-oxides, the paper of Kubota *et al.*³⁵¹ also presents polarographic and ESR data for other azine oxides including the mono- and dioxides of pyrazine, quinoxaline, and phenazine and the oxides of pyridazine, quinoline, and acridine. Their assignment for **105** may be compared with that shown for **22**. On account of the molecular asymmetry,

³⁵⁰ J. M. Fritsch, T. P. Layloff, and R. N. Adams, *J. Am. Chem. Soc.* **87**, 1724 (1965).

³⁵¹ T. Kubota, K. Nishikida, H. Miyazaki, K. Iwatani, and Y. Oishi, *J. Am. Chem. Soc.* **90**, 5080 (1968).

³⁵² M. Itoh and T. Okamoto, *Chem. Pharm. Bull.* **15**, 435 (1967).

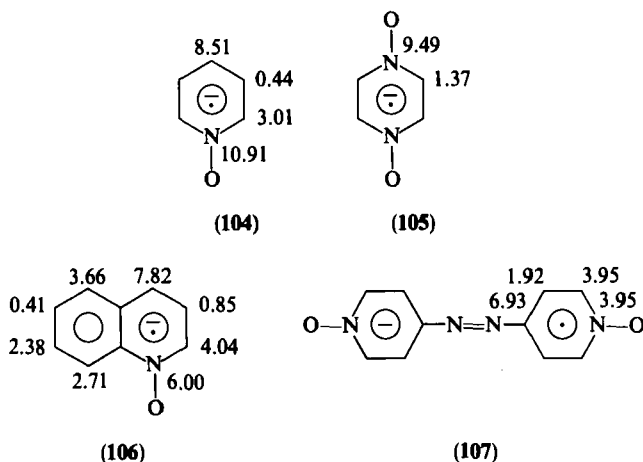
³⁵³ T. Kubota and H. Miyazaki, *Bull. Chem. Soc. Jpn.* **39**, 2057 (1966).

³⁵⁴ V. B. Leont'ev, Yu. V. Kurbatov, D. M. Ivinskii, E. Tuichev, G. V. Kireev, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ.* **206**, 52 (1972); *Chem. Abstr.* **80**, 132508 (1974).

³⁵⁵ E. G. Janzen and J. W. Happ, *J. Phys. Chem.* **73**, 2335 (1969).

³⁵⁶ K. Ezumi, T. Kubota, H. Miyazaki, and M. Yamakawa, *J. Phys. Chem.* **80**, 980 (1976).

no assignment was made for **106**; however, Italian workers have subsequently assigned the spectra of this radical and all its methylated derivatives.³⁵⁷ Here, as in **104** and **105**, the influence of the oxygen ligand does not greatly perturb the spin distribution from that in the anion-radical of the parent heterocycle [cf. splittings in **106** (in gauss) with those for quinoline anion-radical presented in Table II].



Treatment of azobispyridine *N,N'*-dioxide with potassium metal in ethers or with KOH in methanol gives an anion-radical (**107**) for which the hyperfine splittings indicated (in gauss) have been assigned on the basis of spectrum simulation.³⁵⁸

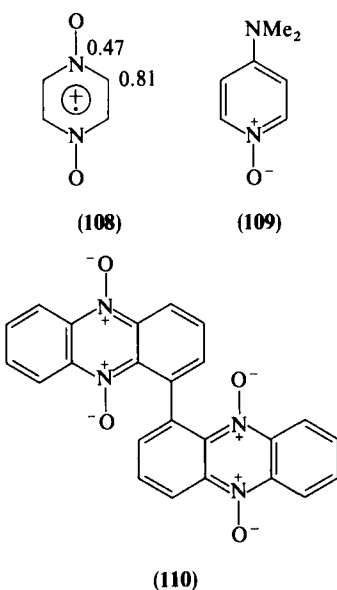
b. Cations. Cation-radicals have been obtained for the *N,N'*-dioxides of pyrazine, quinoxaline, and phenazine.³⁵⁹ Their ESR spectra have been assigned following isotopic substitution experiments. As can be seen from **108**, by comparison with **105**, the spin distribution in the cation-radicals is very different from that in the corresponding anions. In the cation-radicals the spin population is strongly concentrated on the oxygen atoms. (MO calculations and *g*-values support this.³⁵⁹) This confirms that the HOMO and LUMO (and corresponding lower and higher energy MOs) of the diazine dioxides are not "paired" as in even alternant hydrocarbons or, indeed, as in 1,3,6,8-tetraazapyrene whose anion- and cation-radicals (**58** and **103**)

³⁵⁷ L. Lunazzi, A. Mangini, G. Placucci, and F. Taddei, *J. Chem. Soc. B* p. 440 (1970)

³⁵⁸ D. H. Eargle, M. I. Ventura-Batista, and J. Dias da Silva, *Org. Magn. Reson.* **7**, 33 (1975).

³⁵⁹ K. Nishikida, T. Kubota, H. Miyazaki, and S. Sakata, *J. Magn. Reson.* **7**, 260 (1972).

consequently have very comparable spin distributions and hence hyperfine splittings.¹⁹¹



Owing to the high concentration of spin population on oxygen whose abundant isotope has no magnetic moment, the diazine dioxide cation-radicals give relatively narrow ESR spectra (5–12 G).³⁵⁹ The finding that **109** and acridine N -oxide, oxidized anodically, give much broader spectra (50–60 G for **109**) suggests that the nature of the as yet unidentified radicals which are observed is fundamentally different from the cations of present concern.

The cation-radicals of the three diazine dioxides discussed are not persistent. Quinoxaline N,N' -dioxide cation-radical and **108** were observable only at low temperatures. Phenazine N,N' -dioxide cation-radical is observable at room temperature; nevertheless, it dimerizes.³⁵⁹ The product of dimerization has been shown to be **110**, and the rates of dimerization to form **110** and the corresponding product from benzo[*b*]phenazine N,N' -dioxide have been determined.^{360–362} The ESR spectrum of the cation-radical of **110** has also been assigned.³⁶³

³⁶⁰ A. Stüwe, M. Weber-Schäfer, and H. Baumgärtel, *Tetrahedron Lett.* p. 427 (1972).

³⁶¹ A. Stüwe, M. Weber-Schäfer, and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **78**, 309 (1974).

³⁶² A. Stüwe and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **78**, 320 (1974).

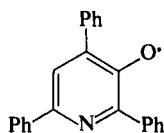
³⁶³ M. Weber-Schäfer and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **78**, 317 (1974).

2. Aryloxyls

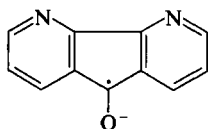
Only two azine aryloxyls have been described, the 2,4,6-triphenylpyridin-3-oxyl (**111**) and its pyrimidin-5-oxyl analog. ESR spectra have been published but not analyzed for these persistent species.³⁶⁴⁻³⁶⁷

3. Ketyls, Semidiones, and Semiquinones

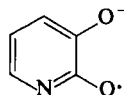
Thermodynamic constants have been determined for the disproportionation equilibria of diazafluorene ketyls, e.g., **112** and its 1,8-diaza isomer, in the presence of each alkali-metal counterion.³⁶⁸



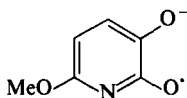
(111)



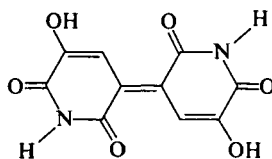
(112)



(113)



(114)



(115)

The ESR spectrum of 10-methylacridin-9-one ketyl was solved during earlier mentioned work on the chemistry of lucigenin.^{258,259} This radical has been implicated in several chemiluminescent systems.³⁶⁹⁻³⁷²

³⁶⁴ H.-J. Teuber, G. Schütz, and H.-J. Gross, *Angew. Chem., Int. Ed. Engl.* **9**, 519 (1970).

³⁶⁵ H.-J. Teuber, G. Schütz, and W. Kern, *Chem. Ber.* **108**, 383 (1975).

³⁶⁶ H.-J. Teuber, G. Schütz, and H. J. Bader, *Justus Liebigs Ann. Chem.* p. 1321 (1977).

³⁶⁷ H.-J. Teuber, H. J. Bader, and G. Schütz, *Justus Liebigs Ann. Chem.* p. 1335 (1977).

³⁶⁸ A. G. Evans, J. C. Evans, P. J. Emes, and S. I. Haider, *J. Chem. Soc., Perkin Trans. 2* p. 1121 (1974).

³⁶⁹ E. A. Chandross and F. I. Sonntag, *J. Am. Chem. Soc.* **86**, 3179 (1964).

³⁷⁰ E. A. Chandross and F. I. Sonntag, *J. Am. Chem. Soc.* **88**, 1089 (1966).

³⁷¹ M. W. Cass, E. Rapaport, and E. H. White, *J. Am. Chem. Soc.* **94**, 3168 (1972).

³⁷² I. Rosenthal and T. Bercovici, *J. Chem. Soc., Chem. Commun.* p. 200 (1973).

In view of the preference of 2- and 4-hydroxypyridines to exist in ketonized forms, it is not surprising that their anion-radicals are essentially ketyls, while the 3-hydroxy isomer exists in the enolic form in isolated matrix.⁹⁶

Addition of two or more hydroxyl groups (or their keto equivalent) into an azine ring gives rise to the possibility of azasemiquinones. The chemistry of these radicals has been studied by Ashworth.^{373,374} One-electron oxidation of 3-hydroxypyrid-2-one or its 5-hydroxy isomer in alkaline conditions leads to the formation of semiquinone anion-radicals, e.g., **113**, which are short-lived but observable by ESR spectroscopy about 0.01 sec after the mixing of reagents in a flow system. Unless alkylated at the 6-position, these primary radicals undergo nucleophilic attack by hydroxylic solvents to give secondary radicals; e.g., **114** is formed in methanol. Ultimately, hydroxypyridones are oxidized to diazadiphenoquinones, e.g., **115**, which are bacterial pigments and which may be reduced to persistent anion-radicals. The very small nitrogen splittings observed for this family of radicals confirm their semiquinone structure: the spin and charge are strongly concentrated on oxygen.

Comparable ketyls and semiquinones are obtainable in the pyrimidine series. Thus, Hayon found that addition of electrons to uracil, during pulse radiolysis, gives anion-radicals which are of a ketyl character.¹³² (See Section III,A,1,d). There have been other radiolytic studies of uracil derivatives.³⁷⁵⁻³⁷⁸ (Patterson and Bansal³⁷⁶ list relevant literature. There has also been a large volume of work on radicals produced from pyrimidines in the solid phase, which is beyond the scope of this article.¹³⁸) It has been found that, under conditions of radiolysis, OH[•] adds to 5-halouracils and 5-nitrouracil at the 5-position. The initial substituent is lost, and the semiquinone **116**, which manifests observable protolytic equilibria, is formed,³⁷⁵⁻³⁸⁰ 5-Nitrouracil has been reduced electrolytically in DMF and found to give a relatively persistent anion-radical. Its 6-methylated analog has the nitro group twisted from the plane of the remainder of the molecule.³⁸¹

The highly oxidized pyrimidine alloxan also gives a semiquinone (**117**).^{136,382}

³⁷³ P. Ashworth, *Biochem. J.* **141**, 577 (1974).

³⁷⁴ P. Ashworth, *Tetrahedron* **32**, 261 (1976).

³⁷⁵ K. M. Bansal, L. K. Patterson, and R. H. Schuler, *J. Phys. Chem.* **76**, 2386 (1972).

³⁷⁶ L. K. Patterson and K. M. Bansal, *J. Phys. Chem.* **76**, 2392 (1972).

³⁷⁷ P. Neta, *J. Phys. Chem.* **76**, 2399 (1972).

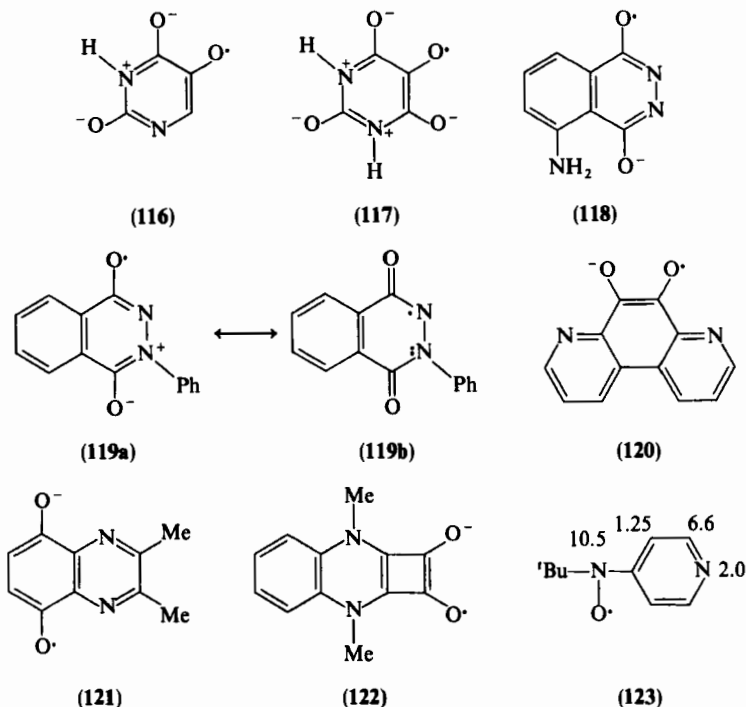
³⁷⁸ P. Neta, *Radiat. Res.* **49**, 1 (1972).

³⁷⁹ P. Neta and C. L. Greenstock, *J. Chem. Soc., Chem. Commun.* p. 309 (1973).

³⁸⁰ H. Zemel and P. Neta, *Radiat. Res.* **55**, 393 (1973).

³⁸¹ M. D. Sevilla, C. Clark, and R. Failor, *Radiat. Res.* **65**, 29 (1976).

³⁸² J. K. Dohrmann, R. Livingston, and H. Zeldes, *J. Am. Chem. Soc.* **93**, 3343 (1971).



The aminophthalazine semiquinone **118** has been shown by Baxendale to be a precursor to the luminescence from luminol induced by OH^\cdot radicals.^{383,384} Structurally comparable "semiquinones," e.g., **119**, have also been synthesized by Pirkle and Gravel.³⁸⁵ The latter radicals persist for several hours; however, in view of the large nitrogen splittings observed, they are correctly regarded as cyclic acylhydrazyls (**119b**) rather than as semiquinones (**119a**).

Other heterocyclic semiquinones which have received attention are **120**, for which Evans and co-workers have studied the variation of ESR parameters with solvent composition,³⁸⁶ and **121**, whose hyperfine splittings have been determined by an Indian group.³⁸⁷ They have also measured the spectra of the 2,3-diphenyl analog and a comparable semiquinone from isoquinoline.³⁸⁷ The heterocyclic semidione **122** has been obtained by Hünig and Pütter as a stage in a suite of redox reactions.³⁸⁸

³⁸³ J. H. Baxendale, *Chem. Commun.* p. 1489 (1971).

³⁸⁴ J. H. Baxendale, *J. Chem. Soc., Faraday Trans. 1* **69**, 1665 (1973).

³⁸⁵ W. H. Pirkle and P. L. Gravel, *J. Org. Chem.* **42**, 1367 (1977).

³⁸⁶ A. G. Evans, J. C. Evans, and E. H. Godden, *J. Chem. Soc. B* p. 149 (1970).

³⁸⁷ M. K. V. Nair, K. S. V. Santhanam, and B. Venkataraman, *J. Magn. Reson.* **9**, 229 (1973).

³⁸⁸ S. Hünig and H. Pütter, *Chem. Ber.* **110**, 2524 (1977).

4. Nitroxyls

Mention has already been made of 1,2,3,4-tetrahydro-3-methyl-2,4-dioxoquinazoline-*N*-oxyl (**29**).³⁸ The only hyperfine splittings that have been resolved are those of the two nitrogen atoms: 6.12 and 2.1 G, respectively.

Exocyclic nitroxyls have been generated by trapping various heterocyclic σ -radicals with 2-methyl-2-nitrosopropane.³⁸⁹ The hyperfine splittings indicated (in gauss) for **123** show that although the spin population is heavily concentrated in the nitroxyl function, nevertheless, significant delocalization of spin into the heterocycle occurs. The reactivity of **123** with various Lewis acids has been investigated.^{390,391}

4-(Hydroxyamino)quinoline *N*-oxide is a carcinogen which is oxidized to give different radicals in different conditions. A structure, unlikely in the author's view, has been assigned to one. Conceivably, a nitroxyl-containing structure is involved here.^{392,393}

5. Radicals from Pteridine, Isoalloxazine, and Related Systems

It is beyond the scope of this chapter to deal in depth with the complex array of radicals deriving from pteridine and isoalloxazine, in particular, those which are derived from naturally occurring pterin and flavin compounds. Accordingly, coverage is restricted to simpler examples and their elementary properties.

a. Pteridine Radicals. The four nitrogens in lumazine (**124**) provide sites for the loss or gain of protons, depending upon the ambient conditions of acidity. Consequently, following the gain of an electron by lumazine, the resultant radical may in principle be anionic, neutral, or cationic, depending upon circumstances. The interrelationships of these species in water have been studied by Moorthy and Hayon, who used the pulse-radiolysis and kinetic absorption spectrophotometry techniques to determine the *pK* values of the various radicals and the kinetics of their formation.³⁹⁴ A similar

³⁸⁹ T. W. Bentley, J. A. John, R. A. W. Johnstone, P. J. Russell, and L. H. Sutcliffe, *J. Chem. Soc., Perkin Trans. 2* p. 1039 (1973).

³⁹⁰ C. T. Cazianis and D. R. Eaton, *Can. J. Chem.* **52**, 2454 (1974).

³⁹¹ C. T. Cazianis and D. R. Eaton, *Can. J. Chem.* **52**, 2463 (1974).

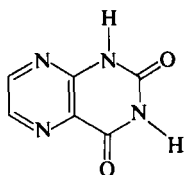
³⁹² N. Kataoka, A. Imamura, Y. Kawazoe, G. Chihara, and C. Nagata, *Bull. Chem. Soc. Jpn.* **40**, 62 (1967).

³⁹³ A. Matsuyama and C. Nagata, *Top. Chem. Carcinog., Proc. Int. Symp., 2nd, 1971* p. 35 (1972); *Chem. Abstr.* **80**, 104674 (1974).

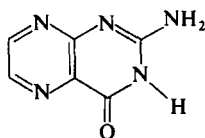
³⁹⁴ P. N. Moorthy and E. Hayon, *J. Phys. Chem.* **79**, 1059 (1975).

study determined the characteristics of the comparable set of radicals derived from pterin (125).³⁹⁵

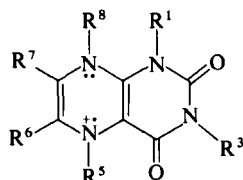
ESR measurements have been made for somewhat more complex species, especially *N*-alkylated radicals.^{396–399} *N*-Alkylation reduces the acid–base capabilities of the system and thus, in principle, should reduce the number of forms of radical. However, it is found that different series of radicals may occur, dependent upon the degree of reduction of the pyrazine ring. Thus, in the lumazine family, cation-radicals both of “dihydro” type (126) and of “tetrahydro” type (127) occur. If R^1 and R^8 are, respectively, H and alkyl, 126 has as conjugate base a neutral radical of type 128. If, however, R^1 and R^8 are, respectively, alkyl and H, the conjugate base is of type 129. Similar situations hold for the conjugate bases of the tetrahydro series (127). Thus, there is a complex array of radicals deriving from 124, depending upon the degree and pattern of its substitution and the extent of its reduction. A parallel situation holds for the derivatives of 125.



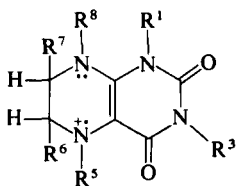
(124)



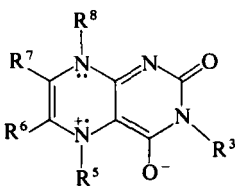
(125)



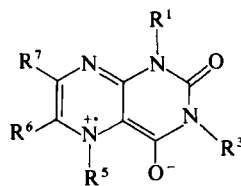
(126)



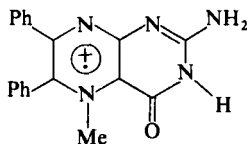
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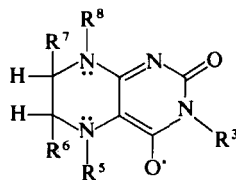
(128)



(129)



(130)



(131)

³⁹⁵ P. N. Moorthy and E. Hayon, *J. Org. Chem.* **41**, 1607 (1976).

³⁹⁶ A. Ehrenberg, P. Hemmerich, F. Müller and W. Pfeleiderer, *Eur. J. Biochem.* **16**, 584 (1970).

³⁹⁷ A. Ehrenberg, P. Hemmerich, F. Müller, T. Okada, and M. Viscontini, *Helv. Chim. Acta* **50**, 411 (1967).

³⁹⁸ A. Bobst, *Helv. Chim. Acta* **51**, 607 (1968).

³⁹⁹ J. Westerling, H. I. X. Mager, and W. Berends, *Tetrahedron* **33**, 2587 (1977).

On account of the lack of symmetry in the pteridine nucleus, each magnetic nucleus has, in principle, its own individual interaction with the electron in the derived radicals, which makes for complex ESR spectra. Progress has been made, however, in comprehending the spin distributions in these radicals. Cation-radicals of the families **126** and **127** were studied by Ehrenberg *et al.*³⁹⁶ This group also studied **130** and its tetrahydro counterpart,³⁹⁷ while Bobst examined the radical from the parent 5,6,7,8-tetrahydropterin.³⁹⁸ Recently, this work has been extended, especially in the lumazine series by Mager and co-workers, who have observed cation-radicals and neutral radicals of both types **128** and **129** and their reduced counterparts.³⁹⁹ The upshot of this considerable body of work is that in the series **126** the spin population is strongly localized in the pyrazine ring, N(5) showing the larger nitrogen splitting, which effect is a consequence of the fusion to the pyrimidine ring and not of any substituent at N(5). Structural variation in the pyrimidine moiety causes minimal effect in the spectra, consistent with very low spin population in that ring. In the more highly reduced series **127** the spin population appears to be confined to the residue of conjugation in the pyrazine ring with the major part localized on N(5). Variation in the structure of the pyrimidine ring again only marginally influences the spectra, indicating that loss of conjugation in the pyrazine ring is not compensated by a major redistribution of spin into the pyrimidine ring. The situation is rather similar in the neutral radicals. N(5) remains the strongest coupling nucleus but, in general, the N(5) coupling constant is smaller in the neutral radicals than in the corresponding cation-radicals (ca. 8 G compared with ca. 11 G), and the decrease does not seem sufficiently compensated by the parallel increase in the N(8) coupling. This may reflect a variation in spin polarization parameters Q with charge type, or it may represent distribution of spin onto non-coupling nuclei such as the ring fusion carbons, or conceivably onto oxygen through contributions such as **131**.

During the oxidative formation of radicals of type **127** from the appropriate tetrahydrolumazine, various reactivities were found.³⁹⁹ Sequential oxidation in formic acid yielded **127** followed by **128**, even when insufficient oxidant was used, implying a disproportionation mechanism. Oxidation of *N*(5)-alkyl side chains to give *N*(5)-acyl substituents was also suggested to account for a further oxidation mode observed.³⁹⁹ Pfeleiderer and co-workers have elucidated radical-mediated pathways in polarographic studies of pterins.⁴⁰⁰

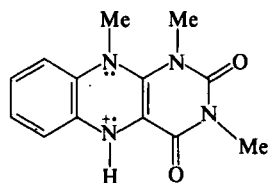
b. Isoalloxazine Radicals. The chemistry of flavine radicals was reviewed by Müller *et al.*⁴⁰¹ The reader is referred to this work and references

⁴⁰⁰ H. Braun and W. Pfeleiderer, *Justus Liebigs Ann. Chem.* p. 1099 (1973).

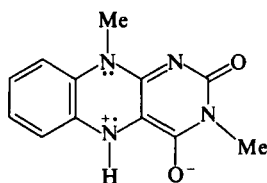
⁴⁰¹ F. Müller, P. Hemmerich, and A. Ehrenberg, *Flavins Flavoproteins, Proc. Int. Symp., 3rd, 1971* p. 107 (1971).

cited therein for a fuller treatment of the topic. Since the latter review, Westerling *et al.* have published work on the ESR properties of cationic isoalloxazine radicals, e.g., **132**⁴⁰² which, it is claimed, supersedes previous interpretations.^{401,403-405} The basis of this claim is the refinement in the procedure of extraction of coupling constants from relatively ill-resolved spectra.⁴⁰² Although the values of coupling constants may now be known with greater certainty, the general conclusions drawn previously about the nature of the spin distribution remain correct.⁴⁰¹ As with the pteridine radicals, there is little spin distribution into the pyrimidine part of the radical. This is confirmed by the negligible effect on spectra of 1- and 3-methylation or of ¹⁵N-isotopic substitution in the pyrimidine ring. Spin is distributed onto the benzo ring, of course.⁴⁰¹

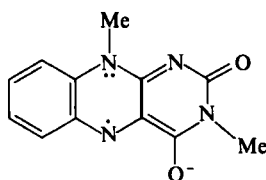
The same conclusions hold for the neutral and anionic isoalloxazine radicals, e.g., **133** and **134**.⁴⁰¹ The neutral radicals have been studied by Ehrenberg



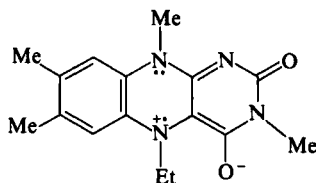
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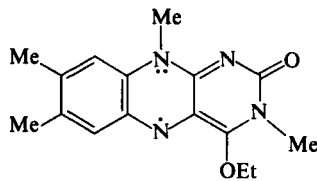
(133)



(134)



(135)



(136)

⁴⁰² J. Westerling, H. I. X. Mager, and W. Berends, *Tetrahedron* **31**, 437 (1975).

⁴⁰³ A. V. Guzzo and G. Tollin, *Arch. Biochem. Biophys.* **103**, 231 (1963).

⁴⁰⁴ A. V. Guzzo and G. Tollin, *Arch. Biochem. Biophys.* **103**, 244 (1963).

⁴⁰⁵ W. H. Walker and A. Ehrenberg, *FEBS Lett.* **3**, 315 (1969).

and co-workers with respect to both ESR and optical properties.^{405,406} Müller *et al.* have distinguished spectroscopically between the two radicals **135** and **136** which are ethylated derivatives of tautomeric forms of the lumiflavin neutral radical and have related these to flavoprotein radicals.⁴⁰⁷ Anionic flavin radicals were studied in detail for solutions in both water and DMF.⁴⁰⁸⁻⁴¹⁰ These radicals form complexes with metal ions; the consequences for the spin distribution of coordination to Cd^{2+} and Zn^{2+} have been investigated.⁴¹¹ ENDOR spectra have been recorded for the zinc complexes of several flavin radicals.⁴¹²

The reactivities of flavin radicals are manifold. Bruice and co-workers have carried out detailed kinetic investigations in the field of flavin chemistry, much of which involves flavin radicals.⁴¹³⁻⁴²⁵ Flavin radicals are key intermediates in the reactions which activate oxygen for autoxidation and for hydroxylation of separate materials.^{426,427}

The preparation of stable flavin radical salts by reduction of the parent heterocycle with UCl_6^- has been described.^{320,321}

Sawyer and co-workers have described the electrochemical characterization of 1-hydroxyphenazine and its 5-methylated derivative (pyocyanine) as flavin model systems and also have measured formation constants for the

⁴⁰⁶ F. Müller, P. Hemmerich, A. Ehrenberg, G. Palmer, and V. Massey, *Eur. J. Biochem.* **14**, 185 (1970).

⁴⁰⁷ F. Müller, M. Brüstlein, P. Hemmerich, V. Massey, and W. H. Walker, *Eur. J. Biochem.* **25**, 573 (1972).

⁴⁰⁸ L. E. G. Eriksson and A. Ehrenberg, *Acta Chem. Scand.* **18**, 1437 (1964).

⁴⁰⁹ L. E. G. Eriksson and A. Ehrenberg, *Arch. Biochem. Biophys.* **110**, 628 (1965).

⁴¹⁰ A. Ehrenberg, F. Müller, and P. Hemmerich, *Eur. J. Biochem.* **2**, 286 (1967).

⁴¹¹ F. Müller, L. E. G. Eriksson, and A. Ehrenberg, *Eur. J. Biochem.* **12**, 93 (1970).

⁴¹² A. Ehrenberg, L. E. G. Eriksson, and J. S. Hyde, *Flavins Flavoproteins, Proc. Int. Symp., 3rd*, 1971 p. 141 (1971).

⁴¹³ S. Shinkai and T. C. Bruice, *J. Am. Chem. Soc.* **95**, 7526 (1973).

⁴¹⁴ S. Shinkai, T. Kunitake, and T. C. Bruice, *J. Am. Chem. Soc.* **96**, 7140 (1974).

⁴¹⁵ S. B. Smith and T. C. Bruice, *J. Am. Chem. Soc.* **97**, 2875 (1975).

⁴¹⁶ T. C. Bruice and Y. Yano, *J. Am. Chem. Soc.* **97**, 5263 (1975).

⁴¹⁷ C. Kemal and T. C. Bruice, *J. Am. Chem. Soc.* **98**, 3955, (1976).

⁴¹⁸ R. F. Williams and T. C. Bruice, *J. Am. Chem. Soc.* **98**, 7752 (1976).

⁴¹⁹ T. C. Bruice and J. P. Taulane, *J. Am. Chem. Soc.* **98**, 7769 (1976).

⁴²⁰ R. F. Williams, S. S. Shinkai, and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 921 (1977).

⁴²¹ T. W. Chan and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 2387 (1977).

⁴²² T. C. Bruice, T. W. Chan, J. P. Taulane, I. Yokoe, D. L. Elliott, R. F. Williams, and M. Novak, *J. Am. Chem. Soc.* **99**, 6713 (1977).

⁴²³ C. Kemal, T. W. Chan, and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 7272 (1977).

⁴²⁴ T. W. Chan and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 7287 (1977).

⁴²⁵ M. Novak and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 8079 (1977).

⁴²⁶ H. I. X. Mager, *Flavins Flavoproteins, Proc. Int. Symp., 5th*, 1975 p. 23 (1976).

⁴²⁷ P. Hemmerich and A. Wessiak, *Flavins Flavoproteins, Proc. Int. Symp., 5th*, 1975 p. 9 (1976).

complexing of the pyocyanine anion-radical by various bivalent metal ions in DMSO.^{428,429}

D. AZOLE RADICALS

Conditions under which anion-radicals are commonly made, e.g., reaction with an alkali metal in an ethereal solvent, are strongly basic. Azoles without a nitrogen substituent in general, therefore, lose the proton from the heteroatom before the electron is added; and, when the latter is added, the product is a dianion radical. Conversely, on oxidation of an azole to give a cation-radical, if the heteroatom is unsubstituted, the proton may be lost, yielding a neutral azolyl radical. Thus, from azoles various radicals may be formed: dianion, anion, neutral, or cation-radicals according to the nature of the substituent at N.

1. Anion-Radicals

Persistent anion-radicals of the monocyclic azoles are not known in solution. Various radical species have been observed in glassy matrix, but there is controversy over their nature.⁴³⁰⁻⁴³² Indole is reported to give a simple anion during γ -irradiation in methyltetrahydrofuran glasses at 77K,⁴³³ whereas others have reported hydrogen adducts in glassy methanol.⁴³⁴ Elving and co-workers have found that imidazole is not reducible cathodically in aqueous media.¹²⁷ Hayon and co-workers have attached electrons to imidazole and histidine in aqueous solution but find that the rate of addition depends strongly on pH; protonated or alkylated imidazoles readily give the neutral conjugate acid of the true anion-radical, or its alkylated derivatives.⁴³⁵ Anion-radicals have been made from nitroimidazoles under various radiolytic conditions and correlations found between their electron transfer properties, their spin distributions, and their biological effects.⁴³⁶⁻⁴³⁸

Carbazoles and other azoles with a comparable extent of conjugation do form anion-radicals which persist in the absence of air. Thus, carbazole

⁴²⁸ M. M. Morrison, E. T. Seo, J. K. Howie, and D. T. Sawyer, *J. Am. Chem. Soc.* **100**, 207 (1978).

⁴²⁹ M. M. Morrison and D. T. Sawyer, *J. Am. Chem. Soc.* **100**, 211 (1978).

⁴³⁰ P. H. Kasai and D. McLeod, *J. Am. Chem. Soc.* **94**, 6872 (1972).

⁴³¹ P. H. Kasai and D. McLeod, *J. Am. Chem. Soc.* **95**, 27 (1973).

⁴³² E. Westhof and W. Flossmann, *J. Am. Chem. Soc.* **97**, 6622 (1975).

⁴³³ R. Arce, M. Charron, and G. A. Simpson, *Radiat. Res.* **68**, 215 (1976).

⁴³⁴ P. J. Baugh, G. O. Phillips, and K. E. Robbins, *J. Chem. Soc., Perkin Trans. 2* p. 347 (1977).

⁴³⁵ P. S. Rao, M. Simic, and E. Hayon, *J. Phys. Chem.* **79**, 1260 (1975).

⁴³⁶ D. W. Whillans, G. E. Adams, and P. Neta, *Radiat. Res.* **62**, 407 (1975).

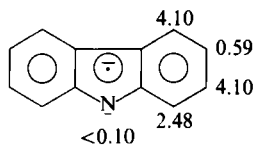
⁴³⁷ C. L. Greenstock, G. W. Ruddock, and P. Neta, *Radiat. Res.* **66**, 472 (1976).

⁴³⁸ P. Wardman and E. D. Clarke, *Biochem. Biophys. Res. Commun.* **69**, 942 (1976).

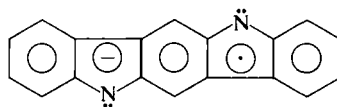
itself forms a dianion-radical (137) whose hyperfine splittings (indicated in gauss) show there is very little spin density at nitrogen in agreement with expectation from Hückel theory.^{439,440} 9-Ethylcarbazole forms a radical-anion showing comparable splittings.⁴⁴¹ The rates of spin transfer between the terminal heterocycles in the anion of 1,2-di(9-carbazyl)ethane have been determined for solutions in THF and DME; they differ by an order of magnitude. Since the solvents are of similar dielectric constant, the reason is ascribed to ion-pairing although the counterion (K^+) manifests no hyperfine splittings in the ESR spectra.⁴⁴¹ The anion of 9-isopropylcarbazole has been described.^{442,443} Hünig and Steinmetzer have described azole anion-radicals belonging to the violene family, e.g., 138.^{444,445}

The dianion-radical of lophine (2,4,5-triphenylimidazole) has been obtained by reduction of the heterocycle by potassium in DME at low temperature. On warming to room temperature, a diamagnetic product results which, in the presence of an excess of potassium, itself gives a radical which is identified as the dianion-radical (139) of 2-phenylphenanthro[9,10-*d*]-imidazole.⁴⁴⁶⁻⁴⁴⁸

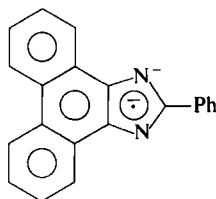
As indicated in an earlier section, the anion-radical initially thought to be 140 was found to be 57.^{129,143,190}



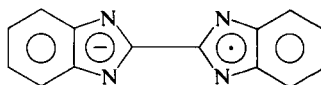
(137)



(138)



(139)



(140)

⁴³⁹ E. G. Janzen, J. G. Pacifici, and J. L. Gerlock, *J. Phys. Chem.* **70**, 3021 (1966).

⁴⁴⁰ N. L. Bauld and J. H. Zoeller, *Tetrahedron Lett.* p. 885 (1967).

⁴⁴¹ D. J. Williams, A. O. Goedde, and J. M. Pearson, *J. Am. Chem. Soc.* **94**, 7580 (1972).

⁴⁴² W. Kloepffer, *Z. Naturforsch., Teil A* **24**, 1923 (1969).

⁴⁴³ W. Kloepffer, G. Kaufmann, and G. Naundorf, *Z. Naturforsch., Teil A* **26**, 897 (1971).

⁴⁴⁴ S. Hünig and H.-C. Steinmetzer, *Justus Liebigs Ann. Chem.* p. 1060 (1976).

⁴⁴⁵ S. Hünig and H.-C. Steinmetzer, *Justus Liebigs Ann. Chem.* p. 1090 (1976).

⁴⁴⁶ K. Volkamer, H. Kiese, and H. Zimmermann, *Tetrahedron* **28**, 5667 (1972).

⁴⁴⁷ H. Kiese, K. Volkamer, and H. Zimmermann, *Ber. Bunsenges. Phys. Chem.* **77**, 108 (1973).

⁴⁴⁸ H. Kiese and H. Zimmermann, *Tetrahedron* **29**, 3043 (1973).

2. Cation-Radicals

Spectroscopic evidence was claimed for a cation-radical from pyrrole following irradiation in a Freon matrix.³⁴¹ Pentaphenylpyrroles are oxidized anodically to relatively persistent cation-radicals whose spectroscopic characteristics, both optical and ESR, have been described.⁴⁴⁹ In general, these radicals are heterocycle-centered; however, when the para substituent in the phenyl rings is NMe₂, the radicals become substituent-centered, i.e., analogous to Würster's Blue. Correspondingly, their persistence is decreased.⁴⁴⁹ Tetraaryl pyrroles form cation-radicals of variable reactivity which have been studied by electrochemical methods.⁴⁵⁰⁻⁴⁵⁴

Recently, evidence for the transient existence of cation-radicals from simple pyrroles and indoles has been furnished by the observation of anodic regiospecific cyanation of these heterocycles.⁴⁵⁵ Both heterocycles are preferentially cyanated at the 2-position. Methyl side chains at these positions are also activated to cyanation and deuteration. Indole cation-radicals have been generated by photoionization in an aqueous medium.⁴⁵⁶ Unsubstituted at N, their lifetime in neutral solution is 10⁻⁶ sec before they lose the N-proton; however, it is longer in more acidic conditions.⁴⁵⁶ The photophysical properties of indole, its cation-radical, and neutral radical have been the subject of a recent theoretical analysis.⁴⁵⁷ On anodic oxidation of 2,3-diphenyl indole in acetonitrile, the initially formed cation-radicals dimerize to a product identified, primarily on the basis of ¹³C NMR, as 3-(5-indolyl)-indolenine (**141**).⁴⁵⁸

Indole cation-radicals are stabilized and rendered persistent by a 3-amino substitution. Thus, Italian workers have characterized aminoindole cations such as **142** where R may be a substituted phenyl or indol-3-yl moiety.⁴⁵⁹⁻⁴⁶¹ In these radicals the principal focus of charge and unpaired spin is exocyclic, as indicated in **142**. On the other hand, cation-radicals such as **143**, which belong to the class of violene radicals and which may be regarded as indole

⁴⁴⁹ G. Cauquis and M. Geniès, *Bull. Soc. Chim. Fr.* p. 3220 (1967).

⁴⁵⁰ M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.* p. 1947 (1971).

⁴⁵¹ M. Libert, C. Caullet, and S. Longchamp, *Bull. Soc. Chim. Fr.* p. 2367 (1971).

⁴⁵² M. Libert, C. Caullet, and J. Huguet, *Bull. Soc. Chim. Fr.* p. 3639 (1972).

⁴⁵³ M. Libert, C. Caullet, and G. Barbey, *Bull. Soc. Chim. Fr.* p. 536 (1973).

⁴⁵⁴ M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.* p. 800 (1974).

⁴⁵⁵ K. Yoshida, *J. Am. Chem. Soc.* **99**, 6111 (1977).

⁴⁵⁶ D. V. Bent and E. Hayon, *J. Am. Chem. Soc.* **97**, 2612 (1975).

⁴⁵⁷ E. M. Evleth, O. Chalvet, and P. Bamière, *J. Phys. Chem.* **81**, 1913 (1977).

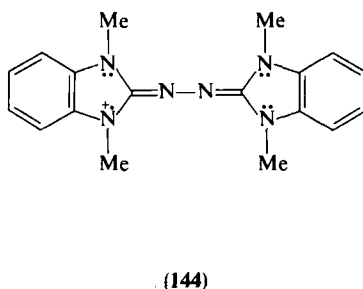
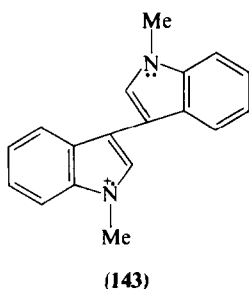
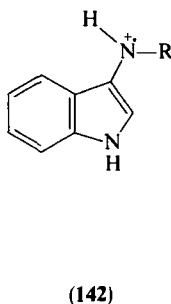
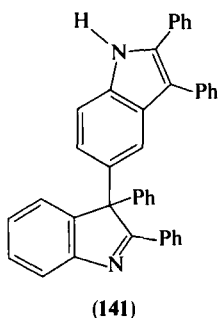
⁴⁵⁸ G. T. Cheek and R. F. Nelson, *J. Org. Chem.* **43**, 1230 (1978).

⁴⁵⁹ P. Bruni, M. Colonna, and L. Greci, *Tetrahedron* **27**, 5893 (1971).

⁴⁶⁰ P. Bruni, M. Colonna, and L. Greci, *Tetrahedron* **29**, 185 (1973).

⁴⁶¹ M. Colonna, P. Bruni, and L. Greci, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis., Rend.* [12] **9**, 33 (1973); *Chem. Abstr.* **80**, 107480 (1974).

cation-radicals with vinylogous amino 3-substituents, are stabilized and persistent species where there is, no doubt, a high spin population at the heterocyclic nitrogen. Hünig and co-workers have studied a range of these materials including benzimidazole analogs such as **144**.^{339,444,445,462-465}



The formation of cation-radicals by carbazoles is well documented. In 1968, it was observed that oxidation of carbazoles with lead tetraacetate in acid conditions led to the formation of the cation-radical of the corresponding 3,3'-dicarbazole. The radicals are persistent and uninfluenced by air or water.⁴⁶⁶ This work was subsequently pursued further, and similar oxidations were effected by other typically single-electron oxidants.⁴⁶⁷ Indications from electrochemical work that the simple cation-radicals are the reactive intermediates appeared about the same time as the initial observation.⁴⁶⁸ This work, too, has been followed-up in depth. Electrochemical

⁴⁶² S. Hünig, G. Kiesslich, F. Linhart, and H. Schlaf, *Justus Liebigs Ann. Chem.* **752**, 196 (1971).

⁴⁶³ S. Hünig, D. Scheutzow, and H. Schlaf, *Justus Liebigs Ann. Chem.* **765**, 110 (1972).

⁴⁶⁴ S. Hünig, D. Scheutzow, H. Schlaf, and H. Pütter, *Justus Liebigs Ann. Chem.* p. 1436 (1974).

⁴⁶⁵ M. Colonna, L. Greci, and P. Bruni, *Gazz. Chim. Ital.* **102**, 527 (1972); *Chem. Abstr.* **78**, 43191 (1973).

⁴⁶⁶ D. H. Iles and A. Ledwith, *Chem. Commun.* p. 498 (1968).

⁴⁶⁷ P. Beresford, D. H. Iles, L. J. Kricka, and A. Ledwith, *J. Chem. Soc., Perkin Trans. I* p. 276 (1974).

⁴⁶⁸ J. F. Ambrose and R. F. Nelson, *J. Electrochem. Soc.* **115**, 1159 (1968).

and spectroscopic techniques have been used to study the oxidation of 76 ring-substituted carbazoles.⁴⁶⁹ It was found that positions 3, 6, and 9 of the carbazole nucleus are the reactive sites, as is expected from Hückel theory. Similar electrochemical data have also been obtained by others.⁴⁷⁰ These electrochemical results complement the observations of Neugebauer and co-workers, who have synthesized carbazoles sterically blocked by *t*-butyl groups at the susceptible ring positions; when so blocked, the radicals become sufficiently persistent for their ESR spectra to be recorded.⁴⁷¹ The ESR spectra of dicarbazole radical-cations have also been recorded.⁴⁷¹ Given the present understanding of the chemistry of simple carbazole radical-cations, the validity of the report that the visible spectrum of the carbazole cation has been recorded must be doubted;⁴⁷² however, the matrix-isolated radical may have been observed.⁴⁷³ Likewise, the ESR spectrum ascribed to the cation-radical of 9-isopropylcarbazole must also be doubted.^{442,443}

The formation of carbazole cation-radicals upon anodic oxidation of di- and triarylamines has been reported.⁴⁷⁴ The main requirement is that the amine used should form a persistent cation-radical (and hence not dimerize) so that it may be oxidized to the dication. It is this species which cyclizes to the carbazole. The carbazole formed is then oxidized to its cation-radical. This is the observed product if the reactive positions in the carbazole are blocked. In general, those substituents which confer persistence on the amine cation-radical are also those which confer it on the carbazole cation-radical.

Despite the reactivity of carbazole cation-radicals, that of 9-ethylcarbazole has been trapped by nucleophiles, e.g., I^- , NO_2^- ,⁴⁷⁵ Thus, iodo and nitro derivatives of 9-ethylcarbazole result, along with 9,9'-diethyl-3,3'-bicarbazole, when 9-ethylcarbazole is oxidized by iodine in the presence of iodide and nitrite.⁴⁷⁵ Oxidation in the absence of nucleophiles, e.g., by nitrosonium tetrafluoroborate, permits the synthesis of the cation-radical fluoroborate salts of the 3,3'-bicarbazoles.⁴⁷⁶ The reactivity of the cation-radical of 9-vinylcarbazole has been reviewed recently.^{11,477}

⁴⁶⁹ J. F. Ambrose, L. L. Carpenter, and R. F. Nelson, *J. Electrochem. Soc.* **122**, 876 (1975).

⁴⁷⁰ W. Lamm, F. Pragst, and W. Jugelt, *J. Prakt. Chem.* **317**, 995 (1975); *Chem. Abstr.* **84**, 89230 (1976).

⁴⁷¹ F. A. Neugebauer, H. Fischer, S. Bamberger, and H. O. Smith, *Chem. Ber.* **105**, 2694 (1972).

⁴⁷² V. E. Sahini, M. Dobrescu, and C. Bendic, *Rev. Roum. Chim.* **16**, 1131 (1971); *Chem. Abstr.* **76**, 29358 (1972).

⁴⁷³ V. I. Skvortsov and M. V. Alfinov, *Opt. Spektrosk.* **41**, 493 (1976); *Chem. Abstr.* **86**, 10238 (1977).

⁴⁷⁴ R. Reynolds, L. L. Line, and R. F. Nelson, *J. Am. Chem. Soc.* **96**, 1087 (1974).

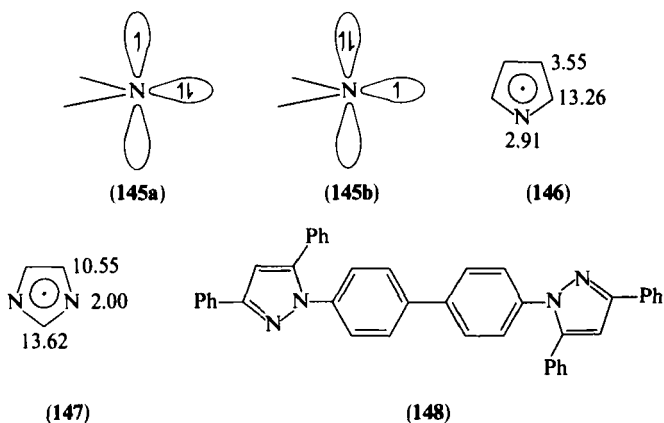
⁴⁷⁵ B. K. Bandlish and H. J. Shine, *J. Heterocycl. Chem.* **12**, 287 (1975).

⁴⁷⁶ B. K. Bandlish and H. J. Shine, *J. Org. Chem.* **42**, 561 (1977).

⁴⁷⁷ P. Hyde and A. Ledwith, in "Molecular Complexes" (R. Foster, ed.), Vol. II, p. 173. Paul Elek, London, 1974.

3. Neutral Radicals

The neutral azole radicals may, in principle, be either π or σ in nature; the trigonal heteroatom may be represented as **145a** for the π state or **145b** for the σ state. Structure **145a** permits the delocalization of the unpaired electron around the rest of the molecular framework, but such N π -interaction would lower the energy of the π -orbital relative to the lone pair orbital, in which case, greater stabilization might be had by delocalizing an electron pair and localizing the unpaired electron in the sp^2 -orbital as in **145b**. This simplistic conclusion could, however, be upset by considering the influence of the remaining electrons within the radical or by allowing geometries other than purely trigonal for the nitrogen. The problem has been discussed in the context of aminyl radicals by Danen and Neugebauer.⁵⁰ There is theoretical controversy over the nature of azolyl radicals. Evleth *et al.*⁴⁷⁸ performed INDO and π -electron SCF MO calculations and concluded that there is ambiguity as to the "predicted" ground-state symmetry. The validity of some of these calculations was questioned by Koenig and co-workers who concluded that pyrrolyl is a π -radical,^{479,480} van der Meer and Ulder inferred, on the basis of calculation, that imidazolyl is, likewise, a π -radical.⁴⁸¹ The



latter conclusions seem confirmed by the experimental results of Samuni and Neta⁴⁸² and Bansal and Sellers.⁴⁸³ These workers have examined the

⁴⁷⁸ E. M. Evleth, P. M. Horowitz, and T. S. Lee, *J. Am. Chem. Soc.* **95**, 7948 (1973).

⁴⁷⁹ T. Koenig, R. A. Wielesek, and J. G. Huntingdon, *Tetrahedron Lett.* p. 2283 (1974).

⁴⁸⁰ T. Koenig, J. A. Hoobler, C. E. Klopfenstein, G. Hedden, F. Sunderman, and B. R. Russell, *J. Am. Chem. Soc.* **96**, 4573 (1974).

⁴⁸¹ K. van der Meer and J. C. C. Mulder, *Chem. Phys. Lett.* **34**, 189 (1975).

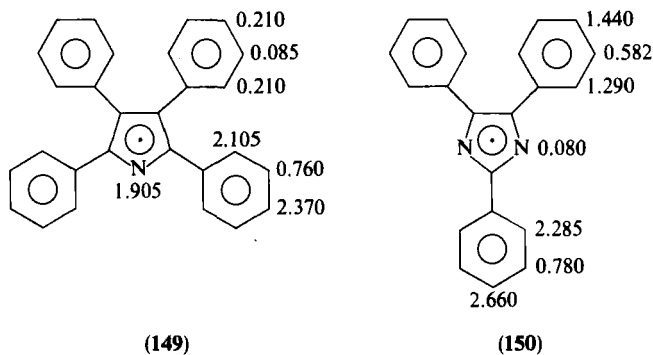
⁴⁸² A. Samuni and P. Neta, *J. Phys. Chem.* **77**, 1629 (1973).

⁴⁸³ K. M. Bansal and R. M. Sellers, *J. Phys. Chem.* **79**, 1775 (1975).

behavior of simple azoles under radiolytic conditions where $\text{OH}\cdot$ attacks the heterocycles. An elimination of water from the adducts ensues to give azolyl radicals whose ESR spectra clearly indicate π -structures **146** and **147** (hyperfine splittings in gauss) for pyrrolyl and imidazolyl. Interestingly, however, more recent ion cyclotron resonance experiments have shown that pyrrolyl is a σ -radical in the low-pressure gas phase.⁴⁸⁴ It thus seems probable that the order of orbital energies in azolyl radicals is as susceptible to variation in real circumstances (and dependent, for example, on the possibility of intermolecular interactions such as hydrogen bonding), as it is computationally where it is dependent on the assumptions and approximations of the particular MO method used.

Both σ and π character have been observed for pyrazolyl radicals. Janssen *et al.* have generated pyrazolyl radicals by thermolysis of *N*-peroxocarboxylates. The radicals thus produced react as *N*- σ -radicals, undergoing phenylation only at nitrogen when produced in benzene and showing pronounced electrophilic character.⁴⁸⁵ On the other hand, the observation of the coupling product **148** formed during the anodic oxidation 1,3,5-triphenylpyrazole implies the involvement of a π -radical.⁴⁸⁶ Calculations by van der Meer and Ulder indicate that pyrazolyl radicals would preferentially be π -species but might persist long enough to react as σ -radicals if generated as such.⁴⁸⁷

Tetraarylpyrrolyl and triarylimidazolyl, e.g., **149** and **150**, are unquestionably π -radicals. On account of the large number of interacting nuclei in these radicals the assignment of hyperfine splittings proved difficult.⁴⁸⁸⁻⁴⁹¹ The



⁴⁸⁴ J. H. Richardson, L. M. Stephenson, and J. I. Brauman, *J. Am. Chem. Soc.* **97**, 1160 (1975).

⁴⁸⁵ J. W. A. M. Janssen, P. Cohen-Fernandes, and R. Louw, *J. Org. Chem.* **40**, 915 (1975).

⁴⁸⁶ I. Tabakovic, M. Lacan, and S. Damoni, *Electrochim. Acta* **21**, 621 (1976).

⁴⁸⁷ K. van der Meer and J. C. C. Mulder, *Tetrahedron* **32**, 1555 (1976).

⁴⁸⁸ S. M. Blinder, M. L. Peller, N. W. Lord, L. C. Aamodt, and N. S. Ivanchukov, *J. Chem. Phys.* **36**, 540 (1962).

⁴⁸⁹ H. Veda, *J. Phys. Chem.* **68**, 1304 (1964).

⁴⁹⁰ M. A. J. Wilks and M. R. Willis, *J. Phys. Chem.* **72**, 4747 (1968).

⁴⁹¹ N. Cyr, M. A. J. Wilks, and M. R. Willis, *J. Chem. Soc. B* p. 404 (1971).

problem seems now to have been satisfactorily resolved by the application of the ENDOR technique to solutions of these radicals.⁴⁹² It is the assignments resulting from this work which are indicated (in gauss) in **149** and **150**.

In order to simulate the ESR spectra of these radicals twist had to be allowed for in the bonds to the phenyl groups. For **149**, the 2(5)-phenyl twist is estimated at ca. 20° and the 3(4)-phenyl twist at ca. 60°; for **150**, coplanarity of the 2-phenyl and imidazole rings is indicated while the 4(5)-phenyl groups are twisted 30° from coplanar.⁴⁹² Concordant results have been obtained for tetraarylpyrrolyl radicals by Broser *et al.* who studied the variation of the *g*-factor with substituents.⁴⁹³

The relationship of **149** and **150** to their various dimers and the photochromic, thermochromic, and piezochromic properties of these materials have attracted much interest. The nature of the dimers formed on oxidation of triarylimidazoles was elucidated by White and Sonnenberg⁴⁹⁴; their properties were studied by groups in America⁴⁹⁵⁻⁴⁹⁹ and Japan.⁵⁰⁰⁻⁵¹¹ The chromism of whatever kind arises from the color of the triarylimidazolyl radicals formed on dissociation of the dimers. Similar conclusions have been reached for dimers of tetraarylpyrrole and similar compounds.^{488,512-516}

⁴⁹² R. D. Allendoerfer and A. S. Pollock, *Mol. Phys.* **22**, 661 (1971).

⁴⁹³ W. Broser, H. Kurreck, D. Rennoch, and J. Reusch, *Tetrahedron* **29**, 3959 (1973).

⁴⁹⁴ D. M. White and J. Sonnenberg, *J. Am. Chem. Soc.* **88**, 3825 (1966).

⁴⁹⁵ L. A. Cescon, G. R. Coraor, R. Dessauer, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.* **36**, 2262 (1971).

⁴⁹⁶ L. A. Cescon, G. R. Coraor, R. Dessauer, A. S. Deutsch, H. L. Jackson, A. MacLachlan, K. Marcali, E. M. Potrafke, R. E. Read, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.* **36**, 2267 (1971).

⁴⁹⁷ R. H. Riem, A. MacLachlan, G. R. Coraor, and E. J. Urban, *J. Org. Chem.* **36**, 2272 (1971).

⁴⁹⁸ A. MacLachlan and R. H. Riem, *J. Org. Chem.* **36**, 2275 (1971).

⁴⁹⁹ R. L. Cohen, *J. Org. Chem.* **36**, 2280 (1971).

⁵⁰⁰ T. Hayashi, K. Maeda, S. Shida, and K. Nakada, *J. Chem. Phys.* **32**, 1568 (1960).

⁵⁰¹ T. Hayashi and K. Maeda, *Bull. Chem. Soc. Jpn.* **33**, 565 (1960).

⁵⁰² T. Hayashi, K. Maeda, and M. Morinaga, *Bull. Chem. Soc. Jpn.* **37**, 1563 (1964).

⁵⁰³ T. Hayashi, K. Maeda, and M. Takeuchi, *Bull. Chem. Soc. Jpn.* **37**, 1717 (1964).

⁵⁰⁴ T. Hayashi and K. Maeda, *Bull. Chem. Soc. Jpn.* **38**, 685 (1965).

⁵⁰⁵ T. Hayashi, K. Maeda, and T. Kanaji, *Bull. Chem. Soc. Jpn.* **38**, 857 (1965).

⁵⁰⁶ T. Shida, K. Maeda, and T. Hayashi, *Bull. Chem. Soc. Jpn.* **42**, 3044 (1969).

⁵⁰⁷ K. Maeda and T. Hayashi, *Bull. Chem. Soc. Jpn.* **42**, 3509 (1969).

⁵⁰⁸ T. Hayashi and K. Maeda, *Nippon Kagaku Zasshi* **90**, 325 (1969); *Chem. Abstr.* **71**, 13038 (1969).

⁵⁰⁹ K. Maeda and T. Hayashi, *Bull. Chem. Soc. Jpn.* **43**, 429 (1970).

⁵¹⁰ T. Shida, K. Maeda, and T. Hayashi, *Bull. Chem. Soc. Jpn.* **43**, 652 (1970).

⁵¹¹ H. Tanino, T. Kondo, K. Okada, and T. Goto, *Bull. Chem. Soc. Jpn.* **45**, 1474 (1972).

⁵¹² R. Kuhn and H. Kainer, *Biochim. Biophys. Acta* **12**, 325 (1953).

⁵¹³ K. Maeda, A. Chinone, and T. Hayashi, *Bull. Chem. Soc. Jpn.* **43**, 1431 (1970).

⁵¹⁴ K. Tomita and N. Yoshida, *Tetrahedron Lett.* p. 1169 (1971).

⁵¹⁵ K. Tomita and N. Yoshida, *Bull. Chem. Soc. Jpn.* **45**, 3160 (1972).

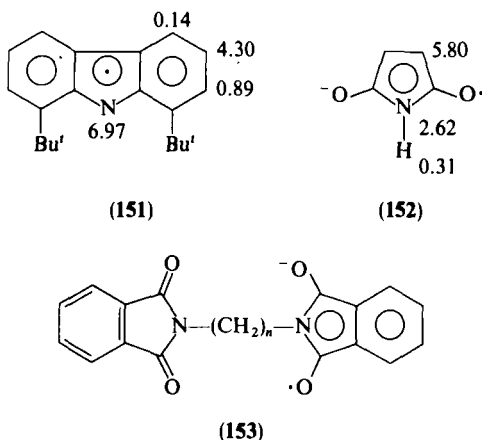
⁵¹⁶ K. Tomita and N. Yoshida, *Bull. Chem. Soc. Jpn.* **45**, 3584 (1972).

Soviet workers and others have studied the kinetics of recombination of the arylimidazolyl and arylpyrrolyl radicals formed after homolysis of the dimers and their dependence upon the aryl substitution pattern.⁵¹⁷⁻⁵²⁵ The anodic oxidation of arylpyrroles and arylimidazoles to cation-radicals which may ultimately lose protons to yield the corresponding azolyl radicals has been studied by several groups.^{450-454,526-529}

Tetrazolynyl radicals, e.g., **11**, were described several years ago.⁵³⁰⁻⁵³² They were reviewed in some detail by Neugebauer with their close relatives, the nonaromatic verdazyls. Subsequently, nothing seems to have been reported for this family of radicals.

Carbazol-9-yl radicals were prepared by Waters and White by thermolysis or photolysis of 9,9'-azocarbazole.⁵³³ They proved to be transient intermediates readily forming 9,9'- or 3,9'- dimers and telomers with similar linkages. They were capable of abstraction of hydrogen from donor solvents. By sterically blocking the reactive sites in the carbazolyl radicals, Neugebauer and co-workers have produced radicals sufficiently persistent for ESR measurements; hyperfine splittings for **151** are given in gauss. The 1,3,7,8-tetrabutylated carbazolyl radical is isolable as a crystalline solid.^{50,471,533} Allendoerfer has reported an ESR and ENDOR study on this latter radical in a glassy toluene matrix.⁵³⁴

- ⁵¹⁷ A. L. Prokhoda and V. A. Kronganz, *Khim. Vys. Energ.* **4**, 176 (1970); *Chem. Abstr.* **73**, 9409 (1970).
- ⁵¹⁸ A. L. Prokhoda and V. A. Kronganz, *Khim. Vys. Energ.* **3**, 495 (1969); *Chem. Abstr.* **72**, 42499 (1970).
- ⁵¹⁹ B. S. Tanaseichuk, A. A. Bardina, and A. A. Khomenko, *Khim. Geterotsikl. Soedin.* p. 1255 (1971); *Chem. Abstr.* **76**, 24519 (1972).
- ⁵²⁰ S. L. Vlasova, B. S. Tanaseichuk, and E. N. Morozov, *Khim. Geterotsikl. Soedin.* p. 1681 (1972); *Chem. Abstr.* **78**, 58173 (1973).
- ⁵²¹ S. L. Vlasova, B. S. Tanaseichuk, L. V. Malysheva, and R. L. Murtazin, *Khim. Geterotsikl. Soedin.* p. 1684 (1972); *Chem. Abstr.* **78**, 71822 (1973).
- ⁵²² S. L. Vlasova and B. S. Tanaseichuk, *Sb. Nauchn. Tr. Ivanov. Energ. Inst.* **14**, 116 (1972); *Chem. Abstr.* **80**, 59296 (1974).
- ⁵²³ A. A. Bardina and B. S. Tanaseichuk, *Sb. Nauchn. Tr. Ivanov. Energ. Inst.* **14**, 111 (1972); *Chem. Abstr.* **80**, 59284 (1974).
- ⁵²⁴ M. A. J. Wilks and M. R. Willis, *Nature (London)* **212**, 500 (1966).
- ⁵²⁵ M. A. J. Wilks and M. R. Willis, *J. Chem. Soc. B.* p. 1526 (1968).
- ⁵²⁶ M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.* p. 345 (1976).
- ⁵²⁷ V. N. Shishkin, B. S. Tanaseichuk, L. G. Tikhonova, and A. A. Bardina, *Khim. Geterotsikl. Soedin.* p. 387 (1973); *Chem. Abstr.* **78**, 167777 (1973).
- ⁵²⁸ W. W. Sümmermann and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **74**, 19 (1970).
- ⁵²⁹ W. W. Sümmermann and H. Baumgärtel, *Collect. Czech. Chem. Commun.* **36**, 575 (1971).
- ⁵³⁰ F. A. Neugebauer, *Tetrahedron Lett.* p. 2129 (1968).
- ⁵³¹ F. A. Neugebauer and G. A. Russell, *J. Org. Chem.* **33**, 2744 (1968).
- ⁵³² F. A. Neugebauer, *Tetrahedron* **26**, 4843 (1970).
- ⁵³³ W. A. Waters and J. E. White, *J. Chem. Soc. C* p. 740 (1968).
- ⁵³⁴ R. D. Allendoerfer, *Chem. Phys. Lett.* **17**, 172 (1972).



4. Oxygenated Azole Radicals and Related Species

a. Radicals from Carbonyl Compounds. Anion-radicals have been described recently for various pyrrole-2,5-diones (maleimides) formed by radiolysis during a wider study of maleamic acids and related species.⁵³⁵ The hyperfine splittings for maleimide itself (152) are given in gauss. By contrast, the benzologs of this radical, those derived from phthalimide, have been known for more than a decade.⁵³⁶⁻⁵³⁸ Szwarc and co-workers have made a recent study of the kinetics of electron exchange between the anion-radical of *N*-*n*-butylphthalimide and the parent heterocycle. The bimolecular rate constant for the process is virtually independent of solvent in polar solvents (ca. $3 \times 10^8 \text{ M}^{-1} \text{ sec}^{-1}$), but the process is slowed in THF, presumably on account of ion-pairing.⁵³⁹ The process of intramolecular electron exchange was also studied for the series 153 where $n = 3 - 16$. The frequency of intramolecular electron transfer for a range of solvents and temperature decreased sharply for $n = 3-5$. It reached a minimum at $n = 6$, rose to a flat maximum for $n = 9, 10$, and then decreased thereafter. Solvent had little influence on the process although the frequency of transfer increased with temperature. Substitution of a polyether chain for the hydrocarbon increased the rate 3-fold. It was concluded that the frequency of exchange reflected the rate of conformational changes.⁵⁴⁰

⁵³⁵ P. B. Ayscough and A. J. Elliot, *J. Chem. Soc., Faraday Trans. 1* **72**, 791 (1976).

⁵³⁶ S. F. Nelsen, *J. Am. Chem. Soc.* **89**, 5256 (1967).

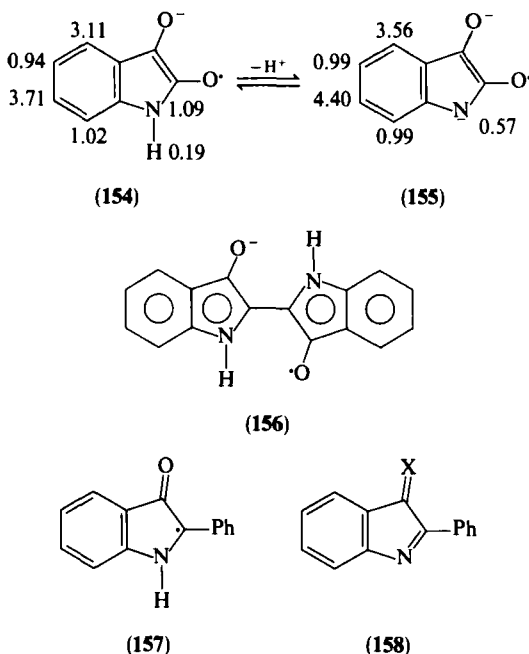
⁵³⁷ M. Hirayama, *Bull. Chem. Soc. Jpn.* **40**, 1557 (1967).

⁵³⁸ R. E. Sioda and W. S. Koski, *J. Chem. Soc.* **89**, 475 (1967).

⁵³⁹ Y. Shimozato, K. Shimada, and M. Szwarc, *J. Am. Chem. Soc.* **97**, 5831 (1975).

⁵⁴⁰ K. Shimada, Y. Shimozato, and M. Szwarc, *J. Am. Chem. Soc.* **97**, 5834 (1975).

Various radicals have been obtained in the indole family. Thus, isatin gives two radicals differing in degree of protonation i.e., **154**, **155**. *N*-Methylisatin gives, as expected, only one radical.⁵⁴¹ The hyperfine splittings and assignment are from recent Rumanian work in which the radicals were produced by electrochemical reduction in DMSO or by potassium reduction in DMF.⁵⁴¹ Essentially identical results had been obtained for the same species by Russell and co-workers several years previously, using a different reducing system.⁵⁴² These workers also obtained several other radicals in the indole family: nitroxides are discussed in the following section. Russell and co-workers had already reported the anion from indigo (**156**) and its conjugate base,^{143,190} interpreting their spectra rather differently from Bruin *et al.*⁵⁴³ Katritzky and co-workers proved the formation of the neutral radical (**157**) on thermolysis of its dimer, 2,2'-diphenyl-2,2'-biindolyl-3,3'-dione.³⁸ Andruzzi *et al.*⁵⁴⁴ produced the anion-radicals of **158** (X = O, NH) on electrolytic reduction of 2-phenyl-3-oxo-3*H*-indoles in DMF; similarly produced were the anions of the *N*-oxides of these materials. Trazza has examined the electrochemical



⁵⁴¹ L. Ciurea, V. E. Sahini, and E. Volanschi, *Rev. Roum. Chim.* **20**, 1029 (1975).

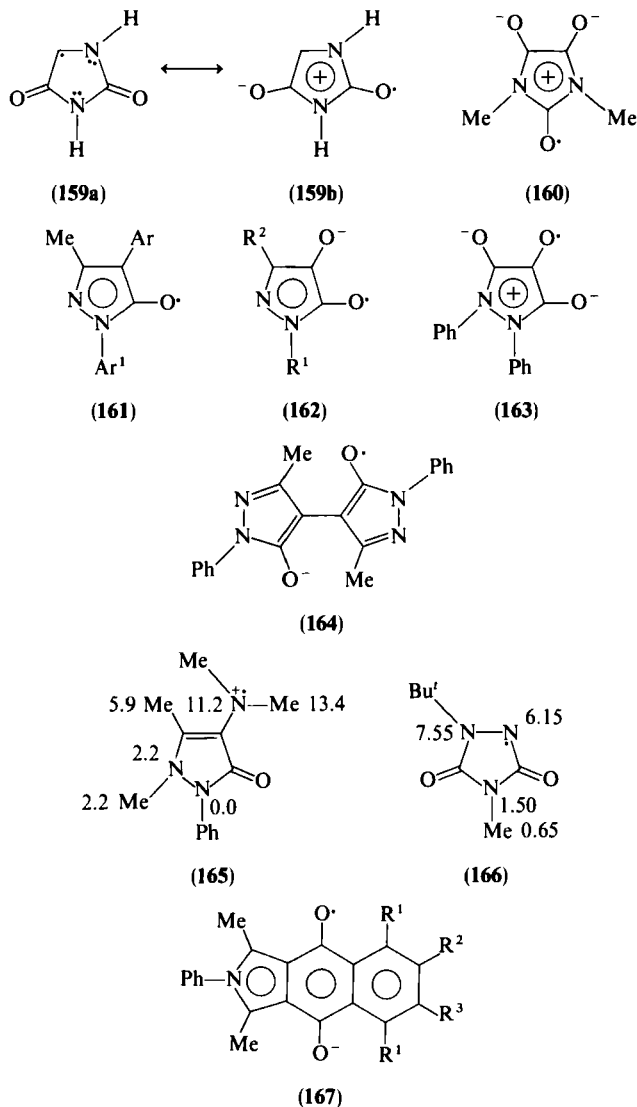
⁵⁴² G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer, and R. Blankespoor, *J. Am. Chem. Soc.* **92**, 2762 (1970).

⁵⁴³ F. Bruin, F. W. Heineken, and M. Bruin, *J. Org. Chem.* **28**, 562 (1963).

⁵⁴⁴ R. Andruzzi, A. Trazza, P. Bruni, and L. Greci, *Tetrahedron* **33**, 665 (1977).

redox behavior of the indolylimino indoleninone **158** [$X = N$ -(indol-3-yl)] and its N -oxide.⁵⁴⁵

Among radicals from diazoles, in the imidazole series hydantoin, methylhydantoin, and thiohydantoin have given various radicals e.g., **159**, differing in degree of protonation, upon radiolysis of aqueous solutions.⁵⁴⁶ Values of



⁵⁴⁵ A. Trazza, *J. Electroanal. Chem. Interfacial Electrochem.* **68**, 97 (1976).

⁵⁴⁶ H. Taniguchi and Y. Kirino, *J. Am. Chem. Soc.* **99**, 3625 (1977).

pK for the various protonolyses were determined. Livingston and Dohrmann generated similarly ionizable radicals from parabanic acid and its *N*-methyl derivative by photolytic methods,³⁸² and Russell *et al.*⁵⁴⁷ obtained a persistent anion-radical (**160**) from dimethyl parabanic acid, notable for the unusually small methyl splitting relative to that of nitrogen.

In the pyrazole series, Katritzky and co-workers prepared the merostabilized pyrazolyl **28**.³⁸ Hüttel *et al.*⁵⁴⁸ have made a series of pyrazolone radicals **161** by thermolysis of the corresponding 4,4'-bipyrazolones. Here the rate of homolysis depends on the nature and number of substituents in the 4-aryl group. It is via radicals like **161** that diastereoisomeric 4,4'-bipyrazolones epimerize on manipulation.⁵⁴⁸ More highly oxidized pyrazoles have given radicals of various types, e.g., **162–164**, by reduction of corresponding keto compounds with base in DMSO.⁵⁴⁹ An anion-radical **162** ($R^1 = \text{Ph}$; $R^2 = \text{Me}$) has been shown to be involved in the autoxidation of 1-phenyl-3-methyl-4-amino-5-pyrazolone at pH > 8.5.⁵⁵⁰

Anodic oxidation of 4-dimethylaminoantipyrene in acetonitrile has yielded a cation-radical (**165**), the ESR spectrum of which indicates the spin population is mainly exocyclic on the tertiary amino group. The second-order rate constant for the decay of **165** was determined; HMO calculation of the spin distribution indicates twist in the C—NMe₂ bond.⁵⁵¹

Neutral radicals in the triazole family, e.g., **166**, which may equally be regarded as cyclic hydrazyls, have been obtained by oxidation of the appropriate urazole.^{552,553} These may be compared with earlier mentioned azine radicals **119**.³⁸⁵

The interpretation of the ESR spectrum of the imidazobenzoquinone (**8**) given by Nair *et al.*^{387,554} has been questioned by Pedulli and co-workers⁵⁵⁵ and an alternative given and justified. The observed equivalence of the nitrogen splittings arises simply owing to the ionization of the N—H proton under the conditions of preparation of the semiquinone. Alkylation at nitrogen imposes nonequivalence of the heteroatoms, as expected. The corresponding imidazo-*o*-benzoquinone was also studied.⁵⁵⁵

⁵⁴⁷ G. A. Russell, J. McDonnell, and C. Meyer, *J. Phys. Chem.* **72**, 1386 (1968).

⁵⁴⁸ R. Hüttel, M. Rosner, and D. Wagner, *Chem. Ber.* **106**, 2767 (1973).

⁵⁴⁹ G. A. Russell and P. Bruni, *Tetrahedron* **26**, 3449 (1970).

⁵⁵⁰ N. F. Usacheva, Yu. G. Oranskii, and M. S. Khaikin, *Zh. Nauchn. Prikl. Fotogr. Kinematogr.* **17**, 416 (1972); *Chem. Abstr.* **78**, 71036 (1973).

⁵⁵¹ H. Sayo and M. Masui, *J. Chem. Soc., Perkin Trans. 2* p. 1640 (1973).

⁵⁵² W. H. Pirkle and P. L. Gravel, *J. Org. Chem.* **43**, 808 (1978).

⁵⁵³ P. L. Gravel and W. H. Pirkle, *J. Am. Chem. Soc.* **96**, 3335 (1974).

⁵⁵⁴ M. K. V. Nair, K. S. V. Santhanam, and B. Venkataraman, *Mol. Phys.* **19**, 585 (1970).

⁵⁵⁵ G. F. Pedulli, A. Spisni, P. Vivarelli, P. Dembech, and G. Seconi, *J. Magn. Reson.* **12**, 331 (1973).

Polarographic studies and ESR spectroscopic measurements have been made on the radicals formed on reduction of 2*H*-benzo[*f*]isoindole-4,9-quinones (**167**).⁵⁵⁶⁻⁵⁵⁸ It is found that the nitrogen and heterocyclic methyl splittings in **167** are approximately proportional to the sum of the Hammett constants for the substituents R^1 , R^2 , and R^3 .⁵⁵⁶

b. Azole Nitroxyls. Hindered pyrroles are capable of formation of persistent nitroxyl radicals, e.g., **168**. Rassat and co-workers described a procedure whereby a suitable 1,4-diketone is cyclized to an *N*-hydroxypyrrole which is subsequently oxidized to the corresponding radical with PbO_2 .^{559,560} Later work by the same group presented electronic and ESR spectroscopic results for **168**. The splittings indicated (in gauss) were assigned on the basis of MO calculation⁵⁶¹; an electrochemical oxidation of 1-hydroxypyrroles was also developed.⁵⁶²

A range of nitroxide radicals has been synthesized in the indole family. Oxidation of *N*-hydroxyisatin with PbO_2 was reported by Russell *et al.* to give the corresponding nitroxide radical (**169**).⁵⁴² Hyperfine splittings were quoted but not assigned other than to nitrogen. Recently, Aurich and Weiss have also quoted hyperfine splittings for **169**, again without assignment of the proton values.⁵⁶³ These latter splittings are indicated (in gauss) for **169**. The considerable discrepancy between the two sets of splittings was ascribed to the solvent difference. Aurich and Weiss have also shown that two sets of similar radicals may be derived from *N*-hydroxyisatin.⁵⁶³ Treatment of this compound with amines yields 3-amino compounds which may be oxidized to radicals, e.g., **170**, with spin distributions very similar to that of **169**. On the other hand, treatment of **169** with primary aliphatic amines yields radicals, e.g., **171**, where the spin population, particularly on nitrogen, is different from **169** and **170**. Colonna and co-workers⁵⁶⁴⁻⁵⁶⁸ have synthesized several bi-indolic radicals, e.g., **172** ($X = H, OH, O^-$) and also **173** ($X = H, O$, or

⁵⁵⁶ E. Müller and W. Dilger, *Chem. Ber.* **107**, 3957 (1974).

⁵⁵⁷ E. Müller and W. Dilger, *Chem. Ber.* **107**, 3946 (1974).

⁵⁵⁸ E. Müller and W. Dilger, *Chem. Ber.* **106**, 1643 (1973).

⁵⁵⁹ R. Ramasseul and A. Rassat, *Bull. Soc. Chim. Fr.* p. 4330 (1970).

⁵⁶⁰ R. Ramasseul and A. Rassat, *Ger. Offen.* 1,917,048 (Cl. C 07d) (1969); *Chem. Abstr.* **72**, 3367 (1970).

⁵⁶¹ R. Ramasseul, A. Rassat, G. Rio, and M.-J. Scholl, *Bull. Soc. Chim. Fr.* p. 215 (1971).

⁵⁶² G. Cauquis, P.-J. Grossi, A. Rassat, and D. Serve, *Tetrahedron Lett.* p. 1863 (1973).

⁵⁶³ H. G. Aurich and W. Weiss, *Tetrahedron* **32**, 159 (1976).

⁵⁶⁴ P. Bruni and M. Colonna, *Tetrahedron* **29**, 2425 (1973).

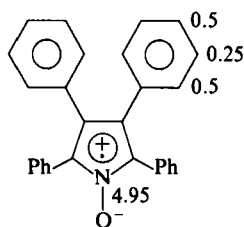
⁵⁶⁵ R. Andruzzi, I. Carelli, A. Trazza, P. Bruni, and M. Colonna, *Tetrahedron* **30**, 3741 (1974).

⁵⁶⁶ P. Bruni and M. Colonna, *J. Heterocycl. Chem.* **11**, 413 (1974).

⁵⁶⁷ C. Berti, M. Colonna, L. Greci, and L. Marchetti, *Tetrahedron* **31**, 1745 (1975).

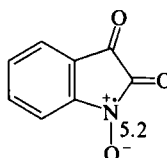
⁵⁶⁸ C. Berti, L. Greci, and L. Marchetti, *J. Chem. Soc., Perkin Trans. 2* p. 1032 (1977).

lone pair). In these papers earlier observations are discussed, interpreted, or rationalized.^{542,569-571} Nonaromatic indolic nitroxyls having saturated indole 2- or 3-positions have also been described.^{564,567,568,572}



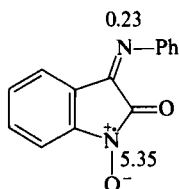
(168)

$a(\text{H})$
2.45
2.15
0.75
0.55



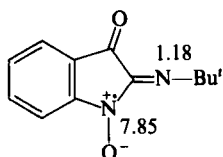
(169)

$a(\text{H})$
2.51
2.28
0.80
0.55

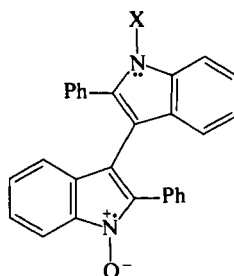


(170)

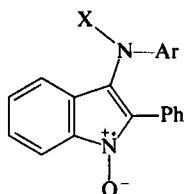
$a(\text{H})$
2.80
2.55
0.55
0.25



(171)



(172)



(173)

⁵⁶⁹ L. Lunazzi, G. Maccagnani, A. Mangini, and G. F. Pedulli, *Tetrahedron Lett.* p. 5807 (1966).

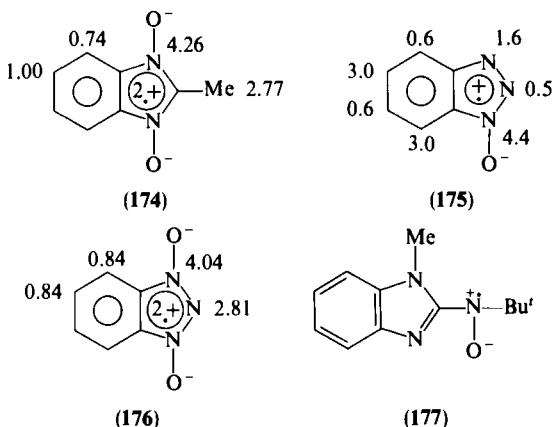
⁵⁷⁰ L. Lunazzi, G. F. Pedulli, G. Maccagnani, and A. Mangini, *J. Chem. Soc. B* p. 1072 (1967).

⁵⁷¹ A. R. Forrester, R. H. Thomson, and G. R. Luckhurst, *J. Chem. Soc. B* p. 1311 (1968).

⁵⁷² P. Bruni and L. Greci, *J. Heterocycl. Chem.* **9**, 1455 (1972).

Carbazole forms a persistent nitroxyl (13) when a solution in benzene containing di-*tert*-butyl peroxide is photolyzed.⁴⁷¹ The radical had been observed earlier in both isotropic and nematic liquid phases and the radical has been theoretically described.^{573,574}

In the imidazole series, an early claim to have observed lophine mononitroxyl was queried when this species and related compounds were unambiguously prepared.⁵⁷⁵⁻⁵⁷⁷ Imidazoles are capable of oxidation at both heteroatoms to give 1-hydroxy-3-oxides. These materials undergo single-electron oxidation to give symmetrical oxyl radicals, e.g., **174**, for which ESR spectra have been reported by several groups.⁵⁷⁸⁻⁵⁸⁰ Those indicated in **174** (in gauss) are due to Aurich and Weiss.⁵⁷⁹ These workers have also assigned the ESR spectra of mono- and dioxyls of benzotriazole **175**, **176**; and Aurich with collaborators has investigated the reactivity of such heterocyclic nitroxides.^{581,582} In addition, they have characterized a series of exocyclic nitroxyls involving azole and related components, e.g., **177**, and have examined their reactivity.⁵⁸³⁻⁵⁸⁶



⁵⁷³ H. R. Falle and G. R. Luckhurst, *Mol. Phys.* **12**, 493 (1967).

⁵⁷⁴ O. Kikuchi, *Bull. Chem. Soc. Jpn.* **42**, 1472 (1969).

⁵⁷⁵ G. Chapelet-Letourneux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.* p. 3283 (1965).

⁵⁷⁶ K. Volkamer, H. Baumgärtel, and H. Zimmermann, *Angew. Chem., Int. Ed. Engl.* **6**, 947 (1967).

⁵⁷⁷ K. Volkamer and H. Zimmermann, *Chem. Ber.* **103**, 296 (1970).

⁵⁷⁸ A. T. Balaban, P. J. Halls, and A. R. Katritzky, *Chem. Ind. (London)* p. 651 (1968).

⁵⁷⁹ H. G. Aurich and W. Weiss, *Chem. Ber.* **106**, 2408 (1973).

⁵⁸⁰ T. E. Gough and R. Puzic, *J. Magn. Reson.* **23**, 31 (1976).

⁵⁸¹ H. G. Aurich and K. Stork, *Chem. Ber.* **108**, 2764 (1975).

⁵⁸² H. G. Aurich, G. Bach, K. Hahn, and G. Küttner, *J. Chem. Res. Synopses* p. 122 (1977).

⁵⁸³ H. G. Aurich and W. Weiss, *Chem. Ber.* **105**, 2389 (1972).

⁵⁸⁴ H. G. Aurich, A. Lotz, and W. Weiss, *Chem. Ber.* **106**, 2845 (1973).

⁵⁸⁵ H. G. Aurich and W. Weiss, *Justus Liebigs Ann. Chem.* p. 432 (1976).

⁵⁸⁶ H. G. Aurich and U. Grigo, *Chem. Ber.* **109**, 200 (1976).

E. RADICALS FROM PURINES, INDOLIZINES, AND CYCLAZINES

1. Purines

There is a large volume of work concerned with the radical species formed in the solid phase when nucleic acid bases and related purines suffer radiation damage. This work is beyond the scope of the present chapter.

Sevilla has obtained an ESR spectrum for the anion-radical of purine formed by electrolysis in DMF at -55° .¹¹⁸ Owing to the asymmetry of the molecule the spectrum was ill-resolved. A better resolved spectrum was obtained for 6-cyanopurine anion radical (178) for which splittings are indicated in gauss. This assignment is tentative and based upon MO calculation. Alternative assignments of the weakly coupling nuclei may be more correct. Nevertheless, it is clear that the unpaired electron in the purine anions is more strongly associated with the azine than with the azole part of the structure, as expected intuitively. The electrochemical reduction of purines in nonaqueous solutions has been studied by two groups.^{587,588} Their results are in essential accord: in general, purines undergo rapid one-electron reduction, and dimerization occurs. One group suggests dimerization of the anions,⁵⁸⁷ while the other suggests that the anion abstracts a proton from unreduced purine to give a neutral radical and purine conjugate base which is electroinactive. The neutral radical is then inferred to be the dimerizing entity.⁴⁸⁸ Both groups agree that in the presence of added acidity the electroreduction becomes a multielectron process. Elving and co-workers also reported the electroreduction of purines in aqueous media. It was concluded that the reduction process involves a series of rapid preprotonations and successive rapid single-electron transfers.¹²⁷ These rapid processes have been investigated by Moorthy and Hayon using pulse radiolysis and kinetic absorption spectrometry.⁵⁸⁹ The hydrated electron and acetonyl radical were used as reducing agents. Reaction rate constants determined at different pH were consistent with the pK values of the substrates and were close to the diffusion-controlled value for the hydrated electron. Optical spectra of the various transient radicals were recorded in appropriate pH ranges, and from these, pK values for the radicals were determined.⁵⁸⁹ No radicals formed by oxidation of purines have been reported although purine ionization processes have been investigated.⁵⁹⁰⁻⁵⁹²

⁵⁸⁷ K. S. V. Santhanam and P. J. Elving, *J. Am. Chem. Soc.* **96**, 1653 (1974).

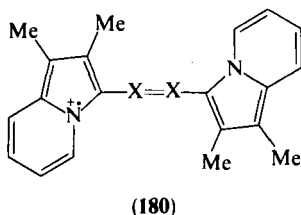
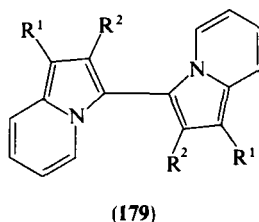
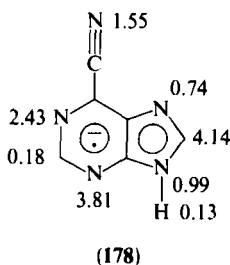
⁵⁸⁸ T. Yao and S. Musha, *Bull. Chem. Soc. Jpn.* **47**, 2650 (1974).

⁵⁸⁹ P. N. Moorthy and E. Hayon, *J. Am. Chem. Soc.* **97**, 3345 (1975).

⁵⁹⁰ V. M. Orlov, A. N. Smirnov, and Ya. M. Varshavsky, *Tetrahedron Lett.* 4377 (1976).

⁵⁹¹ V. M. Orlov, A. N. Smirnov, and Ya. M. Varshavsky, *Mol. Biol. (Moscow)* **11**, 222 (1977); *Chem. Abstr.* **86**, 135060 (1977).

⁵⁹² D. Dougherty and S. P. McGlynn, *J. Chem. Phys.* **67**, 1289 (1977).



2. Indolizines

In contrast to purines, the combination of azole and azine rings in indolizine gives rise to an electron-rich species; as a consequence, only cation-radicals have been reported. The transient existence of a simple cation-radical is implied by the observation of oxidative dimerization of 1,2-dimethylindolizine on treatment with $\text{Fe}(\text{CN})_6^{3-}$ to give **179** ($\text{R}^1 = \text{R}^2 = \text{Me}$).⁵⁹³ The cation-radical of **179** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Me}$) was synthesized by Colonna *et al.*⁴⁶¹ This group also obtained the azaviolene cation-radical **180** ($\text{X} = \text{N}$) and related species.^{594,595}

The redox characteristics of these azaviolenes and of analogs with polyene linkages between the heterocycles have been determined by Hünig and co-workers.^{462,596} The rate constant for the comproportionation reaction yielding **180** ($\text{X} = \text{CH}$) was evaluated as $(6.5 \pm 2.0) \times 10^8 \text{ M}^{-1} \text{ sec}^{-1}$ by Bennion *et al.*⁵⁹⁷ using the temperature-jump technique.

3. Cyclazines

The anion-radical of cycl[3.2.2]azine (pyrido[2,1,6-*cd*]pyrrolizine) (**181**) has been known many years.^{598,599} The observed nitrogen splitting is very

⁵⁹³ S. Hünig and F. Linhart, *Tetrahedron Lett.* p. 1273 (1971).

⁵⁹⁴ M. Colonna, L. Greci, and P. Bruni, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis., Rend.* [12] **8**, 112 (1971); *Chem. Abstr.* **80**, 107666 (1974).

⁵⁹⁵ M. Colonna, L. Greci, P. Bruni, and G. Padovano, *Gazz. Chim. Ital.* **101**, 396 (1971); *Chem. Abstr.* **75**, 140613 (1971).

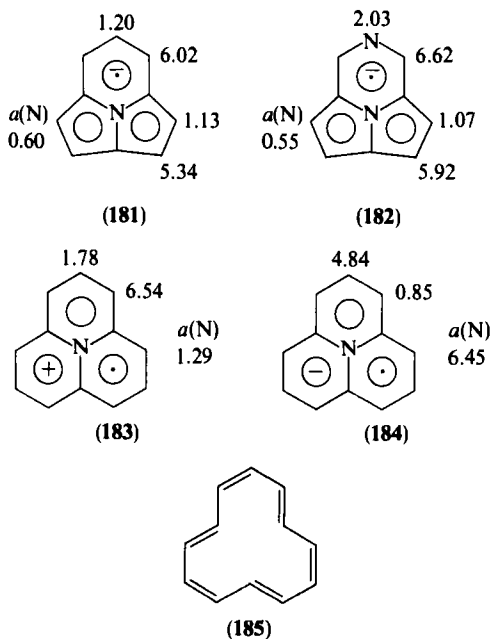
⁵⁹⁶ S. Hünig and F. Linhart, *Justus Liebigs Ann. Chem.* p. 317 (1976).

⁵⁹⁷ B. C. Bennion, J. J. Auburn, and E. M. Eyring, *J. Phys. Chem.* **76**, 701 (1972).

⁵⁹⁸ N. M. Atherton, F. Gerson, and J. N. Murrell, *Mol. Phys.* **6**, 265 (1963).

⁵⁹⁹ F. Gerson and J. D. W. van Voorst, *Helv. Chim. Acta* **46**, 2257 (1963).

small in agreement with HMO theory which predicts that the nitrogen lies in the node of the singly occupied MO. Recently, Gerson and co-workers have examined the anion-radicals of a range of related cyclazines including **182**, an aza analog of **181**. As may be seen from comparable hyperfine splittings (indicated for both radicals in gauss) the singly occupied MO is of the same symmetry in both radicals.⁶⁰⁰ Also studied have been the cation- and anion-radicals of cycl[3.3.3]azine (pyrido[2,1,6-*de*]quinolizine) (**183** and **184**).⁶⁰¹ The contrasting spin distributions in these two radicals were explained by correlating the frontier orbitals of cycl[3.3.3]azine with the degenerate nonbonding orbitals of [12]annulene (**185**). Of these, the anti-symmetric orbital is uninfluenced by interposing the heteroatom, for it lies in its nodal plane, whereas the symmetric orbital mixes strongly with the lone pair orbital of the interposed heteroatom, being thus raised in energy. This analysis, therefore, requires that the HOMO of cycl[3.3.3]azine should correlate with the antisymmetric orbital of [12]annulene and the LUMO with the symmetric orbital. The observed spin distributions in **183** and **184** where the heterocycle's HOMO and LUMO, respectively, are singly occupied confirm this; in particular, the large difference in nitrogen hyperfine splittings and the fact that it is the anion-radical which shows the larger splitting.



⁶⁰⁰ F. Gerson, J. Jachimowicz, B. Kowert, and D. Leaver, *Helv. Chim. Acta* **56**, 258 (1973).

⁶⁰¹ F. Gerson, J. Jachimowicz, and D. Leaver, *J. Am. Chem. Soc.* **95**, 6702 (1973).

IV. Radicals from Phosphorus Heterocycles

A. PHOSPHOLES

Anion-radicals were obtained by alkali-metal reduction of phospholes in ether solvents.⁶⁰² Sodium and potassium gave radicals rapidly whereas lithium failed. The radicals persisted several days at -80° but decomposed above -30° . The persistence of the radicals and their relatively large phosphorus hyperfine splitting, e.g., **186**, by comparison with anion-radicals from phosphines, were interpreted in terms of aromatic character.⁶⁰² The results obtained here contrast with results obtained earlier for **187** where phenyl cleavage and small phosphine-like phosphorus splittings had been observed for the products of attempted anion-radical formation.⁶⁰³ Chemiluminescence on oxidation of the anion-radical of 1,2,5-triphenylphosphole has been reported.⁶⁰⁴

B. PHOSPHORINS

Radicals formed by phosphorins have been reviewed by Dimroth.^{605,606} λ^3 -Phosphorins, e.g., **188**, form both anion- and cation-radicals.⁶⁰⁷ Treatment of **188** with potassium in THF results in the formation of an anion-radical having an ESR spectrum showing a phosphorus hyperfine splitting of 32.4 G and no other fine structure. The anion-radical may be reduced further stepwise, with the uptake of two more electrons. Treatment of **188** with a variety of oxidants leads to the formation of a cation-radical with $a(\text{P}) = 23.2$ G.⁶⁰⁷ Spin polarization parameters were evaluated for phosphorus using the experimental observations on radicals from phospholes and λ^3 -phosphorins.⁶⁰⁸ Gerson and co-workers have carried out a thorough investigation of the anion-radical of λ^3 -phosphorin itself (**189**) in both liquid and glassy phases.⁶⁰⁹ The hyperfine splittings for phosphorus are dependent on temperature and solvent. Those shown (in gauss) for **189** correspond to 20° and generation of the radical by reduction with potassium in DME. The spectra are characterized by a broad linewidth which was shown to be

⁶⁰² D. Kilcast and C. Thomson, *Tetrahedron* **27**, 5705 (1971).

⁶⁰³ A. D. Britt and E. T. Kaiser, *J. Org. Chem.* **31**, 112 (1966).

⁶⁰⁴ E. G. Janzen, W. B. Harrison, and C. M. Dubose, *J. Organo-met. Chem.* **40**, 281 (1972).

⁶⁰⁵ K. Dimroth, *Colloq. Int. C. N. R. S.* **182**, 139 (1970); *Chem. Abstr.* **74**, 22926 (1971).

⁶⁰⁶ K. Dimroth, *Fortschr. Chem. Forsch.* **38**, 1 (1973); *Chem. Abstr.* **79**, 105101 (1973).

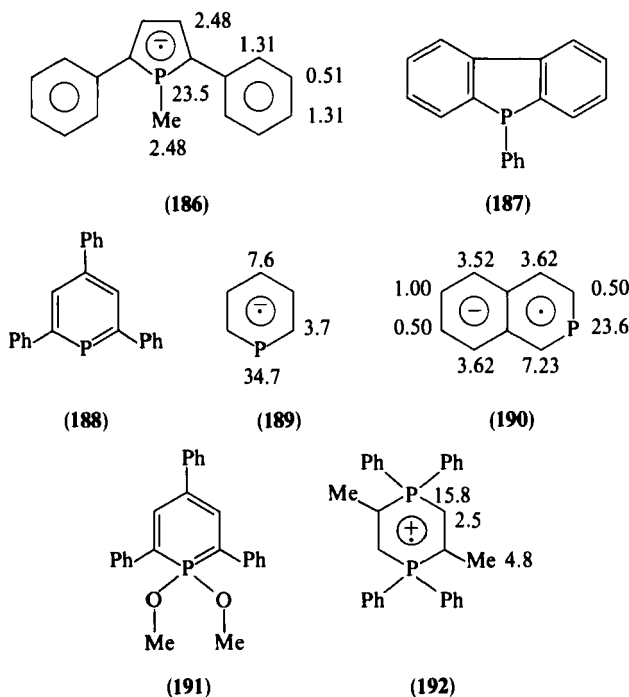
⁶⁰⁷ K. Dimroth and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.* **6**, 445 (1967).

⁶⁰⁸ C. Thomson and D. Kilcast, *Chem. Commun.* p. 214 (1971).

⁶⁰⁹ F. Gerson, G. Plattner, A. J. Ashe, and G. Märkl, *Mol. Phys.* **28**, 601 (1974).

intrinsic to high spin population on phosphorus; the smallest proton splitting was not, therefore, resolved.⁶⁰⁹ Nevertheless, the spin distribution may be compared with that for **1** (Table I). Interestingly, the hyperfine splittings from all the coupling nuclei are resolved for the phosphanaphthalene anion-radical **190** which may be compared with those for isoquinoline anion-radical in Table II.⁶¹⁰

When cation-radicals from λ^3 -phosphorins such as **188** are formed in the presence of nucleophiles and excess of oxidant, further reaction takes place to give λ^5 -phosphorin derivatives, e.g., **191**, generated in the presence of methanol by oxidation of **188** with mercuric acetate.⁶¹¹⁻⁶¹⁴ A crystal and molecular structure determination of a λ^5 -phosphorin shows a planar heterocycle with spd-hybridized phosphorus.⁶¹⁵ Anion- and cation-radicals are also obtainable from the λ^5 -phosphorin system.^{606,611,612}



⁶¹⁰ C. Jongsma, H. G. de Graaf, and F. Bickelhaupt, *Tetrahedron Lett.* p. 1267 (1974).

⁶¹¹ K. Dimroth, A. Hettche, W. Städe, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.* **8**, 770 (1969).

⁶¹² K. Dimroth and W. Städe, *Angew. Chem., Int. Ed. Engl.* **7**, 881 (1968).

⁶¹³ K. Dimroth, N. Greif, W. Städe, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.* **6**, 711 (1967).

⁶¹⁴ K. Dimroth, N. Greif, H. Perst, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.* **6**, 85 (1967).

⁶¹⁵ U. Thewalt, *Angew. Chem., Int. Ed. Engl.* **8**, 769 (1969).

Rieke and co-workers have generated stable cation-radicals by electrochemical reduction of 1,4-diphosphoniacyclohexadiene salts, e.g., **192**.⁶¹⁶⁻⁶¹⁸ The magnitudes of the observed splittings (indicated in gauss) were taken to imply a significant degree of conjugation through the tetravalent heteroatoms.

ACKNOWLEDGMENT

I am indebted to Dr. B. C. Gilbert for helpful comments during the preparation of this article and to my wife for invaluable assistance in the collation of references.

⁶¹⁶ R. D. Rieke, R. A. Copenhafer, A. M. Aguiar, M. S. Chattha, and J. C. Williams, *J. Chem. Soc., Chem. Commun.* p. 1130 (1972).

⁶¹⁷ R. D. Rieke, R. A. Copenhafer, A. M. Aguiar, M. S. Chattha, and J. C. Williams, *J. Electroanal. Chem. Interfacial Electrochem.* **42**, 309 (1973).

⁶¹⁸ R. D. Rieke, R. A. Copenhafer, C. K. White, A. Aguiar, J. C. Williams, and M. S. Chattha, *J. Am. Chem. Soc.* **99**, 6656 (1977).

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The Literature of Heterocyclic Chemistry, Part II

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I. Introduction and General Discussion

A. SCOPE AND ARRANGEMENT

This article is intended as a sequel to that bearing the title "The Literature of Heterocyclic Chemistry"¹ which surveyed and classified the monographs and reviews of the subject for the 20-year period 1945–1965. The survey is restricted (with a few exceptions) to reviews available in English.

The arrangement follows closely that of the earlier chapter, and thus the articles are arranged in a logical order, by subject, using the following criteria: (a) ring size, (b) the number of heteroatoms in the ring, (c) the nature of the heteroatoms, (d) the orientation of the heteroatoms, (e) the degree of unsaturation in the ring, and (f) the topic discussed in the article.

Within each subsection, articles are arranged in date order, commencing with the most recent.

Some general sources and those articles covering topics which cut across this system of arrangement are listed in the next subsection. Final sections cover both those heterocyclic compounds involving "unusual" heteroatoms (any heteroatom other than carbon, nitrogen, oxygen, or sulfur), and alkaloids, drugs, pigments, etc.

For reasons of economy of space, some volumes usually treated in this serial publication as books are styled as periodicals [as recommended by CASSI (Chemical Abstracts Service Source Index of the American Chemical Society)]. For example, *Chem. Heterocycl. Compd.* refers to the Weissberger-Taylor series "The Chemistry of Heterocyclic Compounds" published by Wiley (Interscience); *Alkaloids (London)* is the Specialist Periodical Report, covering that subject, of the Chemical Society (London).

B. GENERAL AND MISCELLANEOUS SOURCES

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J. A. Monick, "Alcohols: Their Chemistry, Properties and Manufacture," pp. 258–273. Van Nostrand-Reinhold, Princeton, New Jersey, 1968.

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D. FOUR HETEROATOMS

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